Evaluating human papillomavirus vaccine introduction in Tanzania and other low-resource settings

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I, Katherine Gallagher confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been transparently indicated.

Signed:

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Contents

Index of Tables

Chapter 1

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Index of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

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Preface

This thesis is structured as a ‘Research Paper Style Thesis’ as per the London School of Hygiene and Tropical Medicine guidelines. The thesis comprises four objectives, which are addressed by four separate studies. The chapters on each objective include a preamble with a detailed description of the role of the candidate. Additional information on the study settings, methods and results that were not included in the manuscripts due to word limits is included after each manuscript, which have been published or submitted for publication in peer-reviewed journals. Publication details and co-author contributions are included on the cover sheets for each manuscript.

Abstract

Evaluation of the success and impact of human papillomavirus (HPV) vaccine introduction and collation of key lessons learnt in low and middle-income countries (LAMICs) is now possible given the number of recent HPV vaccine pilots, or 'demonstration projects', and national programmes. Results may be useful for countries that have not yet commenced implementation of the HPV vaccine and may also be generalizable to future introductions of other pre-adolescent and adolescent vaccines.

This PhD addresses four aspects of HPV vaccine introduction: 1) barriers to adherence to multi-dose vaccine schedules, 2) the potential impact of the HPV vaccine on human immunodeficiency virus (HIV) acquisition, 3) the potential impact of HPV vaccine introduction on other health services, and 4) lessons learnt and recommendations for HPV vaccine implementation in LAMICs.

A systematic review of the published literature on factors influencing multi-dose vaccine adherence in adolescents was conducted. The paucity of published data from LAMICs meant that no geographical restriction was set in the search terms. The majority of research included in the synthesis originated in the United States of America (USA), where race, insurance status and parental healthcare seeking behaviour were found to be predictors of vaccine schedule completion. As vaccination programmes in older children become more established in LAMICs, more research is needed on factors influencing adherence in these settings.

The association between HPV infection and subsequent HIV acquisition was assessed in a nested case-control study using stored cervical samples from previous study cohorts of Tanzanian and Ugandan women. In contrast to previous observational studies that have found an association between HPV infection and HIV acquisition in men and women, we found no evidence of an association between HPV infection, clearance or persistence, and subsequent HIV acquisition. This precluded the calculation of an estimate of the potential population attributable fraction for the effect of HPV infection (and vaccination) on HIV incidence.

Data from health facility register books and interviews with health workers in two regions of Tanzania were analysed to examine the potential impact of HPV vaccination introduction through a demonstration project in Northern Tanzania in 2014 on the provision of routine primary health services. A controlled before-after analysis was carried out on count data of

consultations at facilities involved in HPV vaccine delivery in Kilimanjaro Region, and control facilities in a neighbouring region. Interviews with health workers provided important contextual information. There was no evidence that the number of consultations at the health facilities fell during campaign weeks in intervention facilities compared to control facilities. Utilisation of the health facilities was highly variable. Interviews indicated that the quality of care provided at the facility during vaccination campaigns might be affected by staff absence.

Lessons learnt from 37 LAMICs with at least one year of experience in HPV vaccine delivery were collated from 41 published articles, 124 pieces of unpublished literature, and 27 key informant interviews. Recommendations were formulated in 7 key themes: preparation, communication, delivery, coverage achievements, sustainability, value of demonstration projects and common pitfalls. Lessons were consistent across world regions and included the importance of collaboration during planning between the ministries of health and education, strategies to respond to rumours and challenges encountered during delivery. Key findings were disseminated widely and stimulated on-going supplemental research.

There is now a large evidence base to support the rationale for HPV vaccine introduction and its successful delivery in LAMICs, which currently suffer the heaviest burden of cervical cancer disease in the world. To date, HPV vaccine delivery in low resource settings has achieved high coverage and experienced fewer barriers than expected. It is clear that if funding is available, LAMICs can effectively introduce the HPV vaccine nationally and prevent a high burden of a major and serious disease in women.

Abbreviations

AIN	Anal intraepithelial neoplasia
ANC	Antenatal care
ART	Antiretroviral therapy
CDC	Centers for Disease Control and Prevention (USA)
CI	Confidence interval
CIN	cervical intraepithelial neoplasia
CVL	cervical-vaginal lavage
EPI	Expanded Programme on Immunisation
FP	Family planning
GAP	GARDASIL® Access Program
Gavi	Gavi, The Vaccine Alliance (previously: Global Alliance for Vaccines and Immunisations)
GNI	Gross National Income
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR HPV	high risk human papillomavirus
IARC	International Agency for Research on Cancer
ICO	Institut Catala d'Oncologia
LAMIC	Low and middle-income countries
LIC	Low income countries
LMIC	Lower-middle income countries
LR HPV	low risk human papillomavirus
MITU	Mwanza Intervention Trials Unit
MOE	Ministry of Education
MOH	Ministry of Health
MOHSW	Ministry of Health and Social Welfare (Tanzania)
MRC	Medical Research Council (UK)
MSM	Men who have sex with men
NHS	National Health Service (UK)
NGO	non-governmental organisation
NIMR	National Institute for Medical Research (Tanzania)
OPD	Out-patient department
PAF	population attributable fraction
PAHO	Pan American Health Organization
PATH	PATH (previously: Program for Appropriate Technology in Health)

PIE	post-introduction evaluation
PNC	Post natal care
SAGE	Strategic Advisory Group of Experts on Immunisation
SOP	standard operating procedure
UK	United Kingdom
UMIC	Upper-middle income countries
USA	United States of America
UVRI	Uganda Virus Research Institute, MRC Uganda, Entebbe
VaIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VLP	virus-like particle
WHO	World Health Organization

1 Background

1.1 HPV epidemiology and associated disease

Human papillomavirus (HPV) is a highly prevalent infection in humans. There are 170 known genotypes, 40 of which infect the genital mucosa and are highly transmissible through sexual intercourse[1-3]. Although primarily transmitted through sexual intercourse, there is some evidence of oral-genital and oral-oral transmission[4-7], hand-genital transmission[1], vertical transmission from mother to infant[8,9] and the presence of HPV DNA on perianal skin and in fomites[10,11]. Genital-genital transmission is by far the most common; male to female transmission rates in a study of heterosexual couples with short sampling intervals were between 14 and 87 per 100 person months[1]. Female to male genital transmission rates were between 27 and 187 per 100 person months[1].

The International Agency for Research on Cancer (IARC) has classified HPV genotypes, for which there is sufficient evidence in humans, into categories of carcinogenic risk. High risk genotypes (HR HPV) are defined as the IARC 'carcinogenic' group[12]. A further eight genotypes are classified as 'probably carcinogenic' with insufficient evidence to clarify carcinogenicity due to the low prevalence of single infections of these HPV types in cancer cases [12,13] (Table 1.1).

Table 1.1 IARC classification of HPV genotype carcinogenicity

IARC Classification of carcinogenicity	HPV genotypes
Carcinogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic (Group 2A)[1]	26, 53, 66, 67, 68, 70, 73, 82
Possibly carcinogenic (Group 2B)[2]	30, 34, 69, 85, 97
Unclassifiable[3]	6, 11
Unclassified	40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, 89[4]

[1]Inadequate level of evidence in humans to classify as carcinogenic. [2]Classification is based on phylogenetic similarity to other carcinogenic or probably carcinogenic types with evidence in humans. [3]HPV 6 and 11 cause genital warts in humans; they are of very low prevalence in cancer cases and are used as a reference for classification of other HPV types. [4]HPV 89 previously referred to as CP6108.

Persistent infection with carcinogenic, otherwise called 'high-risk' (HR HPV), genotypes of HPV is now assumed to be the cause of all cases of cervical cancer[14,15]. Recent literature indicates that HPV DNA is also detected in over 70% of cancerous vaginal lesions[16], 20% of vulvar cancers[17], 40% of penile cancers[18], and in both men and women, over 80% of anal cancers[19] and 25-50% of oropharyngeal cancers[13,14,20,21]. Cervical cancer is the third most common cancer in women worldwide[22]. Other HPV-associated cancers are relatively rare, more difficult to research and the natural history of infection and disease is less certain[23,24].

Over 80% of men and women will come into contact with genital HPV at least once in their lifetime[14,25]. However, only a small proportion of these infections will persist to cause cervical intraepithelial neoplasia (CIN) in women, which can progress from CIN grade 1 (CIN1) to CIN of grade three or above (CIN3+) and eventually to cancer[26,27]. In most high-income countries CIN grade 2 or above (CIN2+), identified during screening, is thought to represent a risk of progression to cancer and warrants treatment. Persistence is generally defined as detectable HPV genotype-specific infection lasting $\geq$6months[28]. Clearance is currently defined as the loss of detection of a previous HPV genotype-specific infection[28]. Median length of genital infection with any HPV genotype is 9.8 months[29] and 90% of infections are cleared within 2 years[30]. HR HPV types, on average, persist for longer durations than low-risk types[29,31] and are less likely to be cleared[31]. HPV 16 is the most common genotype present in HPV-associated cancers across anatomical sites[32]. Over 70% of invasive cervical cancers are attributable to genotypes HPV 16 and 18, which persist and progress to lesions quicker than other high-risk types[14]. Almost all cases of genital warts are associated with HPV 6 and 11[14], which also cause (rare) recurrent respiratory papillomatosis[33].

The worldwide prevalence of cervical HPV DNA in women with normal cytology, adjusted for age, region, study and HPV assay characteristics, is estimated to be 10.4% (95%CI 10.2-10.7)[34]. A global review of prevalence data indicates that the detection of HPV DNA peaks in women less than 25 years old then declines, with a small increase again in women over 50 years of age[34-36]. On average, HPV 16 DNA prevalence peaks at younger ages than HPV 18[37]. In one study, detection of HR HPV at baseline and again 2 years later conferred a 12-year absolute risk of CIN3+ of 20%; detection of HPV 16 at two time-points $\geq$2 years apart conferred a 47% risk of CIN3+ 12 years later (95%CI 35-58%)[23]. In developed countries, cervical cancer incidence is highest between age 25 and 35 years i.e. peaks at a younger age range compared with other HPV-related cancers e.g. anal or oropharyngeal cancers[38,39]. Screening and diagnostic services are often limited in developing countries and incidence peaks after age 50[38].

Geographical variation in HPV DNA prevalence and cervical cancer incidence is striking; East African women suffer the highest HPV DNA prevalence in the world (31.7%, 95%CI 29.5-33.8) and experience amongst the highest age-standardised incidence rate of cervical cancer (42.7/ 100,000 women/ year)[22,40]. In Tanzania, amongst cytologically normal, 15-80 year old women from the general population, the prevalence of HR HPV was 14.8%[41]. A study in sexually active, 10-25 year old Tanzanian women revealed 73.5% had detectable HPV DNA of any genotype; 54.7% had HR HPV[42]. The estimated age standardised incidence rate of cervical cancer in Tanzania is 54/ 100,000 women/year, almost quadruple

the global average of 14/ 100,000 women/ year. The age standardised mortality rate due to cervical cancer is 32.4/ 100,000 women/ year, higher than the Eastern Africa average of 27.6 and the worldwide average of 6.8[22,40]. It is estimated that developing world regions carry over 85% of the global burden of cervical cancer mortality[24].

1.1 HPV risk factors

Worldwide, risk factors for HPV infection include women's age (prevalence is highest between the ages of 20-29 years), early age of sexual debut (14 years old or younger), high number of sexual partners (five or more in the past 2 years), current smoking, older age of sexual partner and partner's number of concurrent relationships[43-46]. Condom use does not always prevent HPV transmission and data linking condom use or partner circumcision status with rates of transmission to a partner, or time to HPV clearance, are inconsistent[47-51]. In one study, circumcised men had consistently lower HPV prevalence on the penile shaft or scrotum compared to uncircumcised men[50]; however, evidence for an association between circumcision status and clearance seemed to vary for different HPV types[48]. There may be genetic factors predisposing some groups to HPV persistence and high rates of cervical cancer. Among college attenders tested for HPV at 6 month intervals, African American women were found to have a significantly longer duration of HR HPV infections and reduced clearance compared to European American women[52]. Genetic markers of immune system function may identify women with less efficient immune responses to HPV infection and higher susceptibility to disease[53,54]. However, HPV 16 variants have geographically distinct distributions, potentially vary in pathogenicity and may confound this association[55].

The HIV epidemic in sub-Saharan Africa also affects HPV infection and natural history; cervical cancer is an AIDS defining illness[56]. Detection of cervical HPV DNA rapidly increases after HIV seroconversion in HIV-infected women compared to HIV-uninfected women[57-59]. HIV seropositive women have a greater proportion of multi-genotype infections and more HR HPV types in subsequent cervical lesions than HIV negative women[60]. An increase in the detection of anal and penile HR HPV has also been reported in HIV positive men compared to HIV negative men[61]. These associations could be due to delayed detection of HPV infection acquired at the same time as HIV, increased reactivation of latent virus[62], or increased susceptibility to new infection after HIV acquisition[63]. Cervical or anal HPV is more likely to persist in HIV positive and immunosuppressed women and men, and progress to intraepithelial neoplasia and cancer perhaps due to a deficient T-cell response to the HPV infection[61,64-66]. There is evidence of reduced HPV acquisition, increased rates of HPV clearance and lower rates of cervical cancer among those HIV positive women on anti-

retroviral therapy (ART) with a history of controlled HIV viral load and CD4+ T-cell count >200 cells/ul, compared to HIV positive women not on ART or those who have only recently initiated ART [56,67-70]. However, not all studies support the association between ART duration and HPV infection status in HIV positive women[71] and evidence is not consistent at other anatomical sites. For instance there was no evidence of a reduction in oral HPV prevalence 24 weeks after ART initiation among HIV+ women in the USA[72].

1.2 HPV and HIV acquisition

In addition to its oncogenic potential, HPV may also be an important co-factor in HIV acquisition. A number of recent observational studies have shown HPV to be associated with subsequent HIV acquisition in both men and women[73-78]. There is a plausible biological mechanism for the association: weakened cell adhesion and lesions caused during HPV infection could expose basal layers of the epithelium in the genital tract and form additional HIV entry points[79-81]; HPV infection and the mechanisms involved in clearance may cause an influx of inflammatory cytokines[81] and T-cells[82] creating a favourable environment for HIV invasion. A meta-analysis found an association between detectable HPV DNA and HIV acquisition in 7 of 8 observational studies[83]. There was a two-fold increased risk of HIV acquisition in women with prevalent HPV infection with any HPV genotype (HR: 2.06; 95%CI 1.44–2.94). Similar associations were observed for infection with HR and LR HPV and clearance of any genotype (Table 1.2)[83].

Table 1.2 Meta-analysis results for the association between HPV and HIV acquisition

Category of Infection	Hazard Ratio (95% CI)
Any HPV	2.06 (1.44-2.94)
HR HPV	1.99 (1.54-2.56)
LR HPV	2.01 (1.27-3.20)
Persistent HPV	1.24 (0.59-2.60)
Clearance of HPV	2.09 (1.27-3.44)

Since this meta-analysis, two studies in men have shown a positive association between penile HPV clearance and increased rates of HIV acquisition[84,85]. An associated observation was that men who had cleared penile HPV infections had an elevated density of dendritic cells, target cells for HIV infection, in their foreskin epidermis[85]. In another recent study in KwaZulu Natal, women seropositive for HPV 6, 11, 16, 18 had 2.33 times higher odds of having acquired HIV 12 months later (95%CI 1.61-3.39) than HPV 6, 11, 16, 18 seronegative women, controlling for socio-demographic and sexual behaviour variables[86]. One further observational study in South Africa using cervical samples supported this effect estimate[87].

Estimated population attributable fractions (PAFs) for the HIV burden attributable to infection with any HPV genotype range from 21% to 37%[76,77]. However, deriving these estimates from observational data has limitations. Many of the existing studies have small sample sizes and there may be residual confounding as HPV and HIV are both sexually transmitted and share common risk factors.

1.3 Cervical cancer screening

Cervical cancer can be effectively prevented with early diagnosis and treatment of pre-cancerous lesions[88]. High-income countries have seen dramatic declines in cervical cancer incidence with the implementation of comprehensive screening programmes[14]. The World Health Organization (WHO) recommends that every woman aged between 30-49 years should be screened at least once using HPV testing, visual inspection with acetic acid or Lugol's iodine (VIA or VILI) or cytology. Positive screen results should be referred for treatment if necessary; pre-cancers can be effectively treated with cryotherapy or loop electrosurgical excision procedure (LEEP)[88]. If resources allow, WHO recommends that women with negative screening results should be re-screened every 3-5 years, although the interval could be increased in a vaccinated population[89]. Additionally, HIV positive women may warrant more frequent screening and perhaps starting screening at a younger age[90].

Many LAMICs lack the resources to implement 'screen and treat programmes' nationally, at the required scale[91,92]. Coverage of screening in sub-Saharan Africa is generally low and the majority of the women who seek health care present with advanced stage disease[93,94].

1.4 HPV vaccines

As vaginal, vulvar, penile and anal cancers are relatively rare, HPV vaccines have primarily been developed and marketed for prevention of cervical cancer and genital warts (Table 1.3)[95]. There are currently three safe and efficacious licensed prophylactic HPV vaccines[96,97]. The bivalent vaccine, Cervarix® (GlaxoSmithKline Biologicals s.a.), targets HPV 16 and 18; the quadrivalent vaccine, Gardasil® (Merck & Co.), targets HPV 16, 18, 6, 11; and the nonavalent vaccine, Gardasil-9® (Merck & Co.), targets five further HR HPV types HPV 6, 11, 16, 18, 31, 33, 45, 52, 58. All of the current vaccines are produced using recombinant genotype-specific outer coat viral L1 proteins. The L1 proteins form into non-infectious, virus like particles (VLPs)[95], which are administered together with adjuvants to boost immunogenicity[98]. The proportions of disease attributable to different HPV types are

shown in Table 1.3. Over 90% of genital warts and almost all cases of respiratory papillomatosis are attributable to HPV types 6 and 11.

1.5 HPV vaccine efficacy

Measures of protective efficacy against the endpoint of persistent infection with vaccine genotypes and CIN2+ attributable to HPV 16 and 18, among women seronegative for HPV 16 and 18 at baseline, reach 95% or more for all three vaccines[98,99]. Efficacy is reported to decrease to around 50% for all vaccines in women with evidence of HPV vaccine type infection prior to vaccination (Table 1.4). Bivalent vaccination has been associated with reduced prevalence of oral HPV vaccine types[100]. Quadrivalent vaccine efficacy against genital warts, vulvar (VIN), vaginal (VaIN)[101,102] and anal (AIN) intraepithelial neoplasia has additionally been documented (Table 1.4)[103,104].

Table 1.3 The percentage of HPV-associated disease attributable to HPV genotypes included in the three available vaccines

HPV-associated disease[13,18,21]	Prevalence of HPV in cases	Percentage (95%CI) of cases of HPV+ disease attributable to:		
		HPV 16/18	HPV 6/11/16/18	HPV 6/11/16/18/ 31/33/45/52/58
In women only				
Cervical Cancer[13]	100%	72.8 (70.8-74.7)	72.8 (70.8-74.7)	89.0 (87.5-90.3)
Vulvar cancer[13]	19.3% (16.7-22.0)	73.6 (66.4-79.9)	73.6 (66.4-79.9)	84.0 (77.6-89.0)
Vaginal cancer[13]	71.1% (63.2-78/1)	71.2 (61.8-79.6)	71.2 (61.8-79.6)	89.8 (83.8-94.2)
In men and women				
Anal cancer[13]	87.6 % (81.6-92.1)	87.1 (80.7-92.1)	87.1 (80.7-92.1)	89.8 (83.8-94.2)
Oro-pharyngeal cancers[21]	25.9% (24.7-27.2)	25.6 (14.2-36.9)	25.6 (14.2-36.9)	26.9 (15.8-38.0)
Genital warts[a, 13]	100%	0%	>90%	>90%
In men only				
Penile cancer[b, 18]	33.1% (30.2-36.1)	70.2%	75.4%	84.6%

[a] >90% of genital warts are attributable to HPV 6 and 11.
[b] No confidence intervals for genotype specific attributions were available. HPV 6 and 11 are present as single HPV infections in a small percentage of penile cancer cases[18].

The bivalent vaccine confers some cross-protection against persistent infection and CIN2+ lesions associated with HPV 31, 33, and 45 and a composite of 12 non-vaccine oncogenic types[106-108]. Both vaccines confer a degree of cross-protection against incident infection with HPV 31 and 45, genotypes responsible for 10% of cervical cancer[95,107]. There is now evidence of protective efficacy up to almost 10 years post-vaccination for both the bivalent

and quadrivalent vaccines[98]. The nonavalent vaccine offers comparable protection to the quadrivalent vaccine against persistent infection with genotypes 6, 11, 16, 18 and high vaccine efficacy against infection with the additional 5 HR HPV vaccine types[109].

Table 1.4 A summary of 3 dose vaccine efficacy against disease

Vaccine efficacy (ATP)[a]	**Bivalent vaccine[99,105]**	**Quadrivalent vaccine[99,]**	**Nonavalent vaccine[105]**
CIN 2+	94.9 (87.7-98.4)	100 (94.7-100)	96.7 (80.9 -99.8)
VIN/ VaIN 2+		100 (82.6-100)	
Genital warts		96.4 (91.4-98.9)	
AIN[103]		77.5 (39.6-93.3)	
Vaccine efficacy (ITT)[b]	**Bivalent vaccine**	**Quadrivalent vaccine**	**Nonavalent vaccine**
CIN2+	60.7 (49.6-69.5)	54.8 (40.8-65.7)	Comparable to quadrivalent (0.7% higher protection)
VIN/VaIN 2+		78.5 (55.2-90.8)	
Genital warts		79.5 (73.0-84.6)	
AIN		50.3 (25.7-67.2)	

[a] ATP: According to protocol analysis i.e. vaccine efficacy against HPV vaccine genotype associated disease in women who received 3 doses of vaccine on schedule and were seronegative for HPV vaccine types on vaccination day.
[b] ITT: Intention to treat analysis i.e. vaccine efficacy against HPV vaccine genotype associated disease amongst all women enrolled including women who had received at least one dose of vaccine and those HPV positive at vaccination day.

Rates of seroconversion after natural infection are lower in men than women; the lower antibody titres in men after natural infection are thought to confer lower levels of natural protection[110]. The 3 available vaccines have proven safe and effective against persistent HPV infection in men[111-113], and are now especially advocated for groups at higher than average risk of AIN such as men who have sex with men (MSM)[103]. Three doses of the quadrivalent or bivalent vaccines have proven to stimulate a good immune response in HIV seropositive men and women[114-118].

There is no evidence that any of the available vaccines have therapeutic properties in women infected at the time of vaccination i.e. affect rates of clearance of existing infections[105]. Although initial post-hoc analyses of vaccine trials have indicated that 2 doses may be sufficient to elicit a good antibody response, there are no published trial data on the efficacy of a reduced dose schedule on disease endpoints[119] (See section 1.9: Immunogenicity and dose schedule).

1.6 HPV vaccine safety

All three available HPV vaccines have both proven safe in large vaccine trials. Serious adverse events due to vaccination occurred in <1% of vaccinees and controls in a number of studies[104,105,108,120]. Long-term follow-up of trial participants who had undisclosed pregnancies at the time of vaccination has indicated no adverse effects on pregnancy outcomes[120]. Post-licensure surveillance is on-going in order to identify possible rare adverse events. Despite rumours that generated media attention in 2015[121], a comprehensive review by the European Medicines Agency (EMA) and the WHO Global Advisory Committee on Vaccine Safety (GACVS) confirmed that there was no evidence that rates of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS) or chronic fatigue syndrome (CFS) were higher in vaccinated girls in Europe than would have been expected in the absence of vaccination[122,123].

1.7 HPV vaccine impact

There is now a large quantity of evidence that vaccine efficacy has translated into population-level impact on HPV prevalence with demonstrable cross-protection, herd immunity among older women and boys and declines in disease incidence[124,125]. The prevalence of HPV 16 and 18 in girls less than 20 years old in the USA halved in the 10 years after the introduction of HPV vaccine even though HPV vaccine coverage was as low as 34%[126,127]. Higher coverage (>50%) is thought to be necessary for establishment of herd immunity[126,127]. A comprehensive review estimated that the prevalence of HPV 16 and 18 decreased by 64% across populations with 34-88% vaccine coverage (pooled estimate 0.36; 0.25-0.53)[124]. In the same populations, cross protection against infection with HPV 31/33/45/52/58 has been demonstrated in a 28% decrease in type prevalence (pooled RR 0.72; 0.54-0.96)[128].

A large data linkage study five years after vaccine introduction in Australia found women who had received between 1-3 doses of quadrivalent vaccine had 36% lower rates of CIN3+ compared to unvaccinated women (aHR 0.64; 95%CI 0.45-0.90). This increased to 47% among those who had received the complete vaccine series of 3 doses (aHR 0.53; 0.36-0.77). Three doses of vaccine was associated with 30% lower rates of CIN2+ compared to unvaccinated women (aHR 0.70, 95%CI 0.52-0.94)[129].

Quadrivalent vaccination is associated with an estimated 31% decrease in anogenital warts across studies in the USA, England and Australia in girls age 15-19 years with between 1 and 4 years of follow up post-vaccination (pooled estimate 0.69; 0.60-0.79). There is evidence of herd immunity with decreased HPV prevalence and incidence of warts in older,

unvaccinated groups of men and women in countries with at least 50% vaccine coverage (e.g. England, Scotland, Australia)[124,130,131]. Substantial cost savings are likely in the UK where the National Health Service (NHS) is estimated to spend £17 million per year treating genital warts in men and women[132].

There was no evidence that vaccination contributed to sexual disinhibition post-vaccination in 20 studies, 8 of which had longitudinal designs[133].

It is difficult to quantify the impact of cross-protection induced by the bivalent and quadrivalent vaccines on non-vaccine type HPV associated cancer rates e.g. HPV31/45-associated disease. However, the percentage of disease attributable to HPV genotypes indicates that the nonavalent vaccine could prevent 16% more cervical cancer cases than the quadrivalent vaccine (95%CI14.6-17.8; Table 1.3; ignoring the potential impact of cross-protection)[13]. An analysis of cytological specimens from women aged 15-45 years indicated that nonavalent vaccine strains were associated with 43-55% of CIN1, 70-78% of CIN2 and 85-91% of CIN3 lesions. Compared to the quadrivalent vaccine, the nonavalent vaccine could prevent 23-26% more CIN1 and an additional 36.8% of CIN2+ lesions[134]. Nonavalent vaccination has the potential to substantially decrease the number of patients seeking treatment for CIN2+ and the associated psychological and economic burden of lesion treatment[134].

Although there is no evidence that the current vaccines offer therapeutic properties, such as increased clearance of existing infection, there is some evidence that vaccination after treatment of cervical, vulvar or vaginal neoplasia reduces reinfection and subsequent recurrence of disease by 46% (95%CI 22.5-63.2%)[135]. The greater proportion of cancer cases attributable to oncogenic types other than HPV 16/18 in HIV positive men and women may mean that these individuals could benefit from the greater protection offered by the 9-valent vaccine[60]. Data on immunogenicity of the 9-valent vaccine in this subgroup are not yet available.

Currently the WHO does not recommend vaccination of boys or men due to the low rates of HPV-associated disease and the limited cost-effectiveness of this strategy if high coverage is achieved in girls, given the potential for concurrent herd immunity[136-138]. The USA and Australia are currently the only countries in the world to have introduced HPV vaccination for males (in 2011 and 2013 respectively). Uptake of vaccination among boys between 13 and 17 years of age has been low in the USA (34.6%) with only 13% completing the 3 dose

series[139]. The Australian programme has been more successful with uptake of 72.2% and completion of 83% in boys in 2014[140].

Recommendations for cervical cancer screening have been revised in many countries post-HPV vaccine introduction. Further revisions will be needed if the use of the nonavalent vaccine becomes widespread since this vaccine may protect women from around 90% of cervical cancer.

1.8 HPV vaccine immunogenicity and the 2 dose schedule

The immune correlates of protection for the current prophylactic HPV vaccines are unknown. Evidence suggests HPV primarily induces a humoral immune response, which is often insufficient after a natural infection to prevent re-acquisition in men and women[96,141]. HPV vaccines induce higher avidity antibody responses than natural infection, which peak and then plateau at far higher titres than during natural infection[142,143]. Although initial evidence of immunogenicity and efficacy of all three vaccines against HPV infection and CIN was restricted to 16-23 year old young people, immunogenicity bridging trials illustrated that HPV antibody titres in 10-15 year old vaccinated girls and boys were 1.7-2.7 times higher than those elicited in older vaccinated adolescents[144-146]. The evidence that vaccine efficacy is greater in girls and women who have not been previously infected with the targeted vaccine genotypes[108,147,148]; that HPV infection is acquired rapidly after sexual debut[30,149] and data from immunogenicity bridging studies in pre-adolescents[105], led the WHO to recommend targeting 9-13 year old girls for vaccination[95]. There is evidence that both the bivalent and quadrivalent vaccines confer lasting immune responses for 8-10 years[98,150-152]; individuals who have received the nonavalent vaccine remain under long-term follow-up.

In 2014, the Strategic Advisory Group of Experts on Immunisation (SAGE) revised recommendations for the bivalent and quadrivalent vaccines from a schedule of 3 doses[95], to 2 doses at a 6 month interval for girls aged 9-14 years old[96,153] based on the evidence of non-inferior immunogenicity[142,154,155]. Specific trials are starting in 2016 to assess the immunogenicity of a one-dose schedule. A combined, post-hoc analysis of women enrolled in two trials in Costa Rica and the USA suggested equivalent immune responses after one, two or three doses of the bivalent vaccine and vaccine efficacies of 87.5% (95%CI 60.9-97.1%), 81.2% (59.5-92.3) and 81.4% (59.5-92.3) respectively[156]. However, there are no data on the efficacy of reduced dose schedules against disease end-points[119]. Current recommendations state that girls aged 14-15 years or older and HIV seropositive girls should receive three doses as per original dosage recommendations[96]. Although the vaccines have

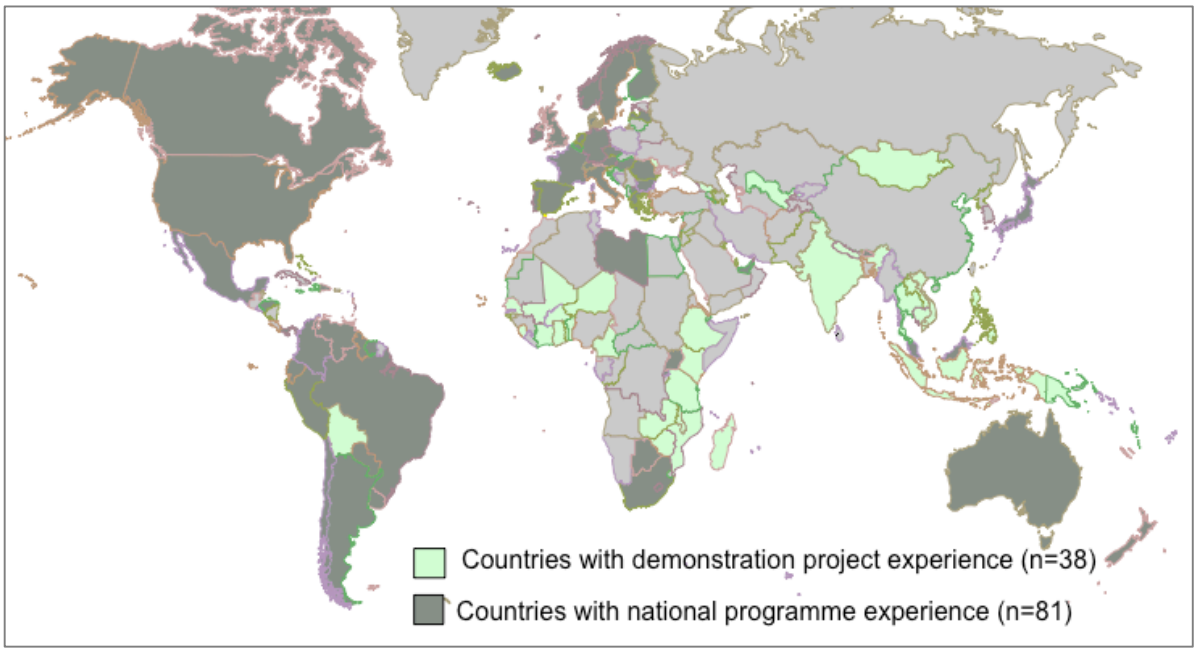
proven safe and immunogenic in HIV positive adults and children[116], there are no data on whether a 2 dose schedule elicits a sufficient immune response in immune-compromised individuals. Despite the requirement for 3 doses in older age groups, some countries have successfully included 'catch-up' vaccination until age 18 or 26 years[157]. There is now a call to increase the availability of catch-up services in order to accelerate the impact of vaccination on the incidence of HPV-related disease worldwide[89].

Co-administration of each of the 3 HPV vaccines with meningococcal conjugate vaccine (MCV4) and/or the Tetanus diphtheria acellular pertussis (Tdap) booster dose has proven safe with non-inferior antibody responses to HPV vaccine when compared to single vaccine administration and adequate serologic responses for all co-administered vaccines[158,159]. Co-administration of the bivalent and quadrivalent vaccines has also proven safe and immunogenic with hepatitis A and B vaccines[159].

1.9 HPV vaccine access and delivery experience

Over 80 countries worldwide introduced the HPV vaccine into their national immunisation schedules between 2006 and May 2016 (Figure 1.1)[160]. Among high-income countries, 78% had introduced the vaccine into their national vaccination schedules and 43% of upper-middle income (UMIC; 23/53) countries had national HPV programmes in place by May 2016. However, only 6% of low (2/31) and 12% of lower-middle income countries (LMIC; 6/51) had national HPV programmes, despite these countries suffering the greatest burden of cervical cancer[98]. High and low-income countries have been able to achieve good HPV vaccine coverage in national programmes e.g. Australia, Scotland, Rwanda, Bhutan[125,161-163]. Some of the lowest HPV vaccine coverage estimates are in the USA where there is no school-based vaccination programme and health providers need further education and reassurance about the vaccine in order to consistently recommend it[164].

Figure 1.1 HPV vaccination experience worldwide, May 2016



Vaccine introduction in developing countries was initially difficult because of the high vaccine purchase price and the cost of delivering the vaccines. Demonstration projects were designed in order to enable countries to pilot gender-specific delivery to the often-novel target group in a small region(s) of the country. Between 2007 and 2012, a number of low and middle income countries (LAMICs) were able to conduct demonstration projects in select districts/regions with vaccine provided from the GARDASIL® Access Program (GAP), manufacturer donations, non-governmental organisations (NGO), and/or government funds; however, there were limited, to no, funds available to enable scale-up to national programmes. Between 2007 and 2012, the GAP demonstration projects, managed by Axios Healthcare Development, were the most numerous (n=20) and were enabled by large donations of vaccine by Merck & Co. pharmaceuticals; no funds for the cost of delivery were provided[165]. Typically these projects targeted around 5000 girls within a country.

Two low-income countries, Bhutan and Rwanda, received direct manufacturer donations to initiate national HPV vaccination programmes in 2010 and 2011 respectively[166,167]. Middle income countries in the Americas benefitted from a low negotiated vaccine price through the Pan American Health Organization (PAHO) revolving fund, which enabled national programmes to begin in 2011, elsewhere there was a significant lag in national HPV vaccine introduction[168,169].

To accelerate vaccine introduction in low-resource settings, in 2012, Gavi, The Vaccine Alliance (Gavi), commenced offering support for HPV vaccination demonstration projects

and national programmes in 53 Gavi-eligible countries[170]. Eligible countries had to have an average Gross National Income (GNI) per capita of USD 1580 or less over the last three years and over 70% coverage for routine childhood vaccines[170]. Gavi support, which is undergoing revisions in 2016 in order to encourage more national HPV vaccination programmes, was available for 2 year demonstration projects or national programmes. However, support for HPV vaccine national programmes was only available if the country had prior experience of delivering a multi-dose vaccine to adolescents with high coverage[171]. Demonstration projects had to target a single age cohort e.g. 9 year old girls, or a single grade in school. Vaccine and some funds for delivery and evaluation were provided for target populations (of up to 15,000 girls) across all selected districts. Countries were encouraged to conduct an assessment of available adolescent health interventions and to test integrating HPV vaccine delivery with another intervention in the second year of the project. To qualify for support for a national programme after a demonstration project, the project needed to have achieved more than 50% HPV vaccine coverage of the target population[171].

2 Study rationale, aims and objectives

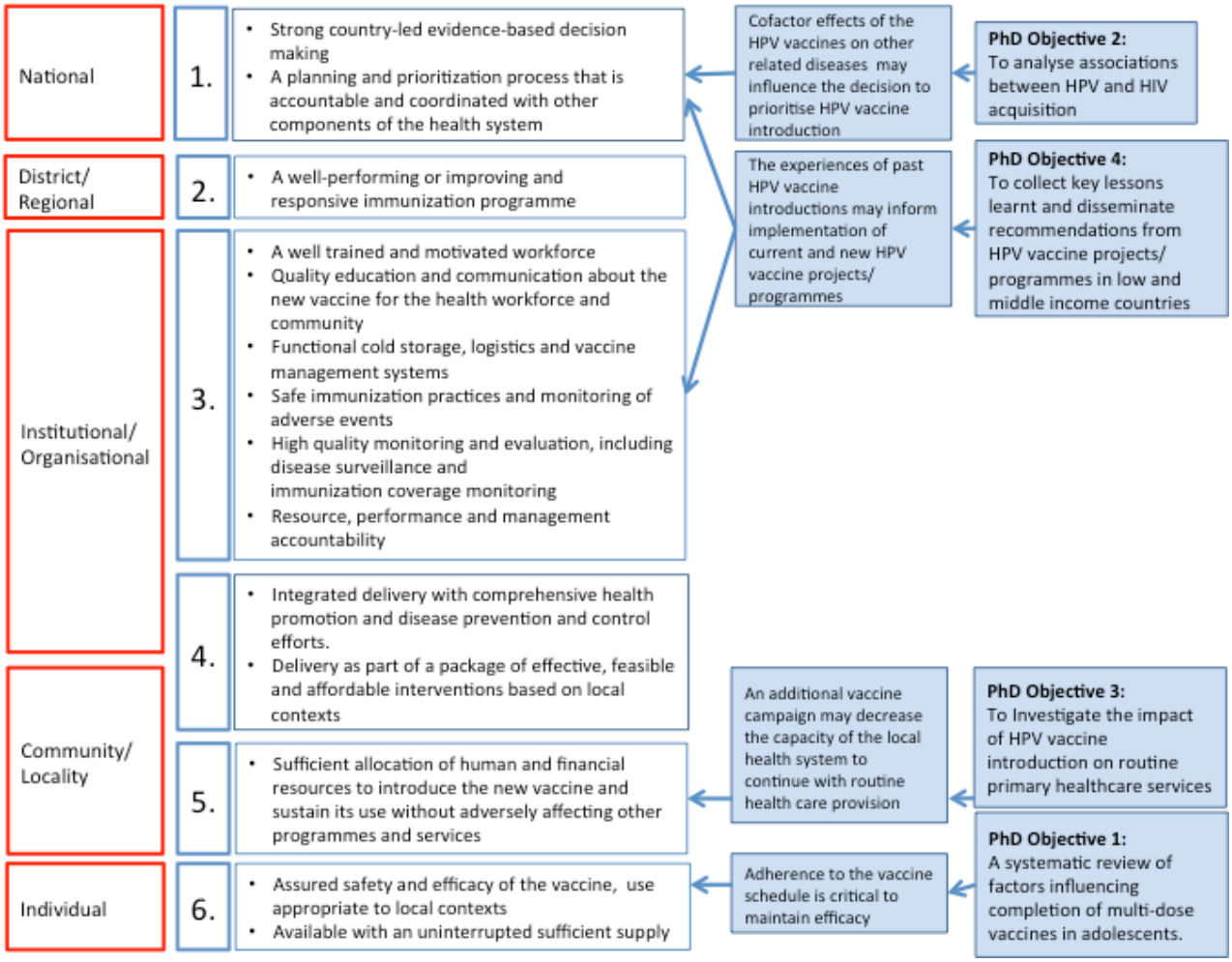
2.1 Study rationale: The gaps in knowledge around HPV vaccine introduction

The vaccination of 70% of 12-year-old girls against HPV 16 and 18 in the 72 poorest countries over 10 years could avert 3 million premature deaths[172]. The WHO has outlined 6 'guiding principles' to achieve successful new vaccine introduction (Figure 2.1)[173]. This PhD addressed specific gaps in HPV vaccine introduction knowledge relevant to four of the guiding principles.

Guiding principle six states new vaccine introduction should ensure safe and efficacious vaccine delivery with an uninterrupted supply[173]. Currently, two doses of HPV vaccine are thought to be necessary to ensure vaccine efficacy in 9-13 year old girls. Adherence to the vaccine schedule has proved problematic in some high-income countries where only 13-43% of girls who received the first dose received the final dose[127,174]. Adherence in low-income settings could potentially be more difficult than high-income settings[168]. Although factors affecting HPV vaccine acceptability[175-178], and coverage[161,179-181] have been previously documented and include awareness, access to vaccination sites, and perceived importance of the vaccine; factors affecting adherence to multiple dose vaccine schedules have been less studied. Identification of factors affecting the completion of vaccine schedules in adolescents may aid the development of strategies to improve completion and prevent low

adherence in future vaccine introductions. However, previous reviews of completion rates have focused on developed countries[182-185], have non-systematic searches[186,187] or are out-dated[180]. A systematic review of factors affecting adherence to multi-dose vaccine schedules (including, but not exclusive to, HPV vaccine) in adolescents was conducted for *objective 1 (Chapter 3; Manuscript 1).*

Figure 2.1 The six guiding principles for new vaccine introduction and the PhD objectives (adapted from the 2014 WHO framework for new vaccine introduction[173])



Guiding principle one states new vaccine introduction should be governed by strong country-led decision making[173]. At the national level, introduction of HPV vaccine requires political commitment for it to remain a funding and resource priority[188,189]. Additional beneficial effects of HPV vaccine introduction, such as potentially strengthening the health system, forming a platform for other interventions, or conferring effects on other prevalent diseases, could help prioritisation where other relevant economic evaluations are insufficient or irrelevant. If the

association between HPV infection and subsequent HIV acquisition that has been documented in small observational studies[83] can be replicated, studies to assess the potential impact of HPV vaccine on HIV acquisition could follow. Cost-effectiveness of vaccination in sub-Saharan Africa would increase if the HPV vaccine decreased subsequent HIV acquisition by even a small amount. Evidence of an association between HPV and subsequent HIV may increase political will to introduce HPV vaccine nationally, especially in countries with high HIV burden. A study of the association between HPV infection and subsequent HIV acquisition was conducted for *objective 2 (Chapter 4; Manuscript 2).*

The availability of sufficient funding and resources in order that vaccine introduction does not adversely affect other services is a new focus in the 2014 WHO framework and is included in guiding principle five[190]. Detrimental effects of child health campaigns on routine services have been documented in the Gambia and Cameroon[191-194]. A systematic review of the impact of new vaccine introduction on health systems found little information on LAMICs or service provision[195]. It is plausible that the additional workload of a multi-dose vaccine delivered in schools could affect routine health care in settings with limited numbers of health professionals. Even some high-income countries experienced a shortage of health workers to deliver the new vaccine in schools; in Australia a shortage of school-nurses led to the development of an additional task-force[196]. In LAMICs, task shifting to lower cadre staff, or acceleration of combination vaccines may be preferable to introducing additional intensive campaigns using the limited supply of qualified staff[195,197]. As Tanzania proceeded to introduce the HPV vaccine in a large region of northern Tanzania with Gavi support, the impact of introducing HPV vaccine on routine care and health worker workload in Tanzania was examined for *objective 3 (Chapter 5; Manuscript 3).*

The advent of Gavi support for HPV vaccine has allowed many more LAMICs to gain experience in HPV vaccine delivery. Some delivery strategies[161] and methods of sensitisation[175] have been documented. A guide to developing educational materials for HPV vaccine is available[198]. A broad review of some of the early GAP demonstration projects is available[165,179]; and interviews have outlined potential challenges and barriers to HPV vaccine delivery in seven countries[168]. However, despite these reviews, and a few country-specific publications[166,199,200], there has been no collation of experience to date and little published data on the most recent Gavi demonstration projects. There is no central resource for other countries to learn from as they are designing and planning their own demonstration projects or national introductions. A comprehensive synthesis of existing data from HPV vaccine introductions, including technical reports, WHO post-introduction evaluations (PIEs),

and additional data collection interviews was performed to formulate recommendations for HPV vaccine introduction in LAMICs for *objective 4 (Chapter 6; Manuscript 4).*

2.2 Aims of the studies in this thesis

The overall aim of this PhD was to evaluate how to effectively deliver and maximise the impact of HPV vaccine in low-resource settings by investigating: 1) barriers to adherence of multi-dose vaccine schedules, 2) the potential effect of the HPV vaccine on subsequent HIV acquisition, 3) how an HPV vaccine campaign impacts other health services and 4) lessons learnt from LAMICs with implementation experience.

2.3 Objectives

This thesis is structured around four primary objectives and manuscripts:

1. To conduct a systematic literature review of factors influencing adherence to multi-dose vaccines in adolescents.
    - Manuscript 1- Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review (Published; BMC Public Health[201])
2. To analyse associations between HPV and HIV acquisition.
    - Manuscript 2 - The association between HPV and subsequent HIV acquisition in Tanzanian and Ugandan women: a nested case-control study (Published; Journal of Infectious Diseases[202])
3. To investigate the impact of an HPV vaccine campaign on routine primary healthcare service provision in Kilimanjaro region, Tanzania
    - Manuscript 3 - The impact of an HPV vaccine campaign on routine primary health care services and health workers in Tanzania (Submitted; International Journal of Epidemiology and Community Health)
4. To collect the lessons learnt from HPV vaccine demonstration projects and national programmes in LAMICs and investigate reasons why countries with a high disease burden have not yet decided to introduce HPV vaccine, to inform recommendations for future HPV vaccine introductions.
    - Manuscript 4 – Lessons learnt from human papillomavirus vaccination in low- and middle-income countries (Submitted; WHO Bulletin)

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Funding for fieldwork to investigate the effect of HPV vaccination on routine healthcare was awarded from the LSHTM Travelling Scholarship Fund (£5,000) and The Chadwick Trust small grants scheme (£5,000). A total of £10,000 enabled the full extent of data collection from 63 health centres, and 19 in-depth interviews with health workers.

The collation of lessons learnt from HPV vaccine projects and programmes in LAMICs was funded by the Bill & Melinda Gates Foundation and awarded in November 2014 (PI: Deborah Watson-Jones). A supplement award was then received from the Foundation for the period January 2016 - September 2016.

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3 Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review (PhD objective 1)

3.1 Preamble

A systematic review of the literature on factors influencing adolescents' adherence to multiple-dose vaccines was conducted to inform existing vaccination programmes and preparation for future new vaccination programmes for this age group e.g. an HIV, herpes or dengue vaccine. This manuscript describes the literature on factors influencing adherence to or 'completion' of multi-dose vaccines in adolescents for objective 1 of the PhD.

I conceptualized and designed this review with advice from Deborah Watson-Jones and David Ross. I conducted the database searches, designed the screening tools and exclusion criteria and performed the initial screened of the abstracts. I trained two other screeners to conduct the second screen of abstracts. I wrote the first draft of the synthesis of results and the manuscript and led on the responses to reviewers.

The manuscript is formatted in accordance with journal requirements (BMC Public Health).

As this manuscript has already been published, a copy of the fully formatted 'pdf' as published is included after the manuscript text.

I have presented a poster of this work at the following conference:

- The 29th International Papillomavirus Conference ('HPV 2014'); August 20-25th 2014; Seattle, Washington State, USA. **'Factors influencing adherence to multi-dose vaccines in adolescents: a systematic review'.** K Gallagher, DA Ross, D Watson-Jones

3.2 Coversheet: Manuscript 1

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Katherine E Gallagher
Principal Supervisor	Deborah Watson-Jones
Thesis Title	Evaluating human papillomavirus vaccine introduction in Tanzania and other low-resource settings

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMC Public Health		
When was the work published?	February 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	YES	Was the work subject to academic peer review?	YES

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed, conducted the search, instructed a second reviewer, screened the abstracts, extracted the data, synthesised the findings and wrote the first draft of the manuscript.

Student Signature: K Gallagher **Date:** 16/06/16

Supervisor Signature: DL Watson-Jones **Date:** 16 June 2016

3.3 Copyright agreement

3.4 Manuscript 1 - Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review.

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Abstract

Background: Completion of multiple dose vaccine schedules is crucial to ensure a protective immune response, and maximise vaccine cost-effectiveness. While barriers and facilitators to vaccine uptake have recently been reviewed, there is no comprehensive review of factors influencing subsequent adherence or completion, which is key to achieving vaccine effectiveness. This study identifies and summarises the literature on factors affecting completion of multi-dose vaccine schedules by adolescents.

Methods: 10 online databases and four websites were searched (February 2014). Studies with analysis of factors predicting completion of multi-dose vaccines were included. Study participants within 9-19 years of age were included in the review. The defined outcome was completion of the vaccine series within 1 year among those who received the first dose.

Results: Overall, 6159 abstracts were screened, and 502 full texts were reviewed. Sixty one studies were eligible for this review. All except two were set in high-income countries. Included studies evaluated human papillomavirus vaccine, hepatitis A, hepatitis B, and varicella vaccines. Reported vaccine completion rates, among those who initiated vaccination, ranged from 27% to over 90%. Minority racial or ethnic groups and inadequate health insurance coverage were risk factors for low completion, irrespective of initiation rates. Parental healthcare seeking behaviour was positively associated with completion. Vaccine delivery in schools was associated with higher completion than delivery in the community or health facilities. Gender, prior healthcare use and socio-economic status rarely remained significant risk or protective factors in multivariate analysis.

Conclusion: Almost all studies investigating factors affecting completion have been carried out in developed countries and investigate a limited range of variables. Increased understanding of barriers to completion in adolescents will be invaluable to future new vaccine introductions and the further development of an adolescent health platform.

Keywords

Vaccines and immunization; immunization programmes; vaccination completion; barriers; adolescent health services.

Background

In the past decade there has been an increase in the number of new vaccines licensed worldwide[1,2] and in the accessible funding for vaccine introduction to low-resource settings through the founding of the Gavi, The Vaccine Alliance, in 2000[3]. Multi-dose vaccines in the WHO recommended Immunization schedule for adolescents are listed in **Table 3.1**; WHO defines adolescence as age 10-19 years inclusive. National vaccine schedules can depart from WHO recommendations, e.g. 2 doses of hepatitis A and meningococcal conjugate vaccines (MCV4) are offered to adolescents in the USA[4]. Although recommended for administration at birth, hepatitis B vaccine (HBV) is routinely offered to older children and adolescents if not previously immunised[5]. In settings where varicella is seen as a public health priority WHO recommends 2 doses of varicella vaccine, with the first dose at 12-18 months and up to 4-month interval between doses[6,7]. The most recently licensed multi-dose vaccines are the human papillomavirus (HPV) vaccines. In 2014, HPV vaccine recommendations were revised by WHO SAGE from a schedule of 3 doses[8], to 2 doses at a 6 month interval in girls less than or equal to 15 years of age[9,10] based on evidence of non-inferior immunogenicity[11,12].

At present, evidence suggests multiple doses of HBV, HPV, and varicella vaccines are needed for efficacious protection against disease in adolescents[5,9,13,14]. However, completion of the vaccine dose series, defined as receipt of the final dose within 1 year of the first dose, has proven challenging in some settings. Completion rates of HPV vaccine were lower than 30% in the first years of introduction in the USA[15,16]. Addressing specific difficulties in administering vaccines to adolescents will be invaluable for implementation of future adolescent vaccines and further developing adolescent health services.

The currently available reviews of factors influencing completion focus solely on selected developed countries[1,17-19], have non-systematic searches[20,21] or need updating[22]. This systematic review describes factors that have been investigated for their effect on multi-dose vaccine adherence in adolescents to aid development of interventions to improve adherence.

Methods

Search Strategy

A comprehensive set of search terms was built around: 1) childhood/adolescence; 2) vaccination/immunisation; 3) adherence/completion. Articles with at least one term from each topic were identified. Search terms were informed by the Cochrane Child Health Group recommended terms for adolescents or school children[23] and included international spelling variations (**Supplementary Table 3.1**). Multi-dose vaccines administered to adolescents were identified through the Centers for Disease, Control, and Prevention (CDC)[6,24], and the WHO list of prequalified vaccines[25]; however, search terms were not limited to these vaccines.

Medline, Embase, Global Health (Ovid SP), Popline, Web of Science, Africa Portal, Africa-wide information, ADOLEC, Cochrane, Open Grey databases, and PATH, Gavi, and WHO websites were searched in February 2014. No publication date restriction was set. Publications, abstracts and conference proceeding were eligible for inclusion. All texts were collated and reviewed using Endnote X7 (Thompson Reuters); automated and manual de-duplication was performed.

Inclusion Criteria

Inclusion criteria for consideration of studies were outlined in a protocol a-priori as per PRISMA guidelines[26] (**Table 3.2**). The title and/or abstract of each article were reviewed in the first instance by a single reviewer (KG). Modelling studies, immunogenicity/efficacy trials were excluded. Two reviewers (KG, SM/EK) screened the abstracts. Any study including a vaccine for which more than one dose was administered to persons 9-19 years old in a routine setting within 1 year was considered for inclusion. The WHO definition of adolescent (10-19 years old) was widened to include 9 year olds to include all participants in HPV vaccine studies (WHO recommended for 9-13 year olds). Inclusion criteria were independently applied to full texts by 2 authors (KG, SM/EK) (**Figure 3.1**)[26].

Data extraction

Data were extracted by 2 authors (KG, EK) into separate forms on Microsoft Excel 2010. Article selection and data extraction discrepancies were resolved through discussion. Data on the study population, setting, vaccine, rates of completion and the factors investigated were extracted alongside descriptive, univariate and multivariate results, as applicable.

Assessment of bias

An assessment of bias was recorded on the data extraction form for each study using criteria outlined in the Cochrane tool for assessment of bias in intervention and epidemiological studies[27]. Selection bias and information bias were assessed alongside the potential for confounding.

Data synthesis

Heterogeneity in study methods, population, context and classification of exposure variables, led to a descriptive synthesis. Groups that initiated and completed the recommended vaccine schedule within 1 year were compared to non-completers who only initiated.

Results

Of the 502 full texts reviewed (**Figure 3.1**), 61 articles were eligible for inclusion (**Table 3.3**). Included articles reported completion rates for HPV (3 dose completion ranged from 27%[15] to over 90%[28]), HBV (27% completion before a school mandate was introduced in California[29] to 95% in a school-based programme in Canada[30]), varicella and hepatitis A vaccine (HAV). In the USA, the two dose series of varicella vaccine was completed within 1 year in 35.9% of adolescents and 2 doses of HAV were completed in 40-48%[31]. Searches returned no articles on completion of conjugate meningococcal vaccine, despite a multi-dose policy in the USA[32]. For the purposes of this review we have focused on results from multivariate analyses or qualitative findings. Data availability by country and vaccine is displayed in **Table 3.4**.

Individual level factors

Age

The association between age and completion was investigated in 31 articles. Multivariate analyses of at least 2 age categories within the age range of 9-19 years were conducted in 20 studies, in the USA (n=17), Canada[33], France[34], and Australia[35]. Age recommendations vary across countries; results must be interpreted in context.

There is some evidence that completion rates decrease as age of vaccine initiation increases for HPV vaccine, HAV, and HBV[15,31,36-38]. In the USA, the HPV vaccine recommended age range is between 11-26 years; five studies state similar results among Medicaid enrolees, adjusting for insurance, race, region and year, 17 year

olds were 0.84 times as likely to complete HPV vaccine compared to 11 year olds (95%CI 0.74-0.95)[15]. Among attendees of an urban hospital, in adjusted analyses, 14-17 year olds had 0.71 the odds of completion HPV vaccine when compared to 9-13 years olds (95%CI 0.59-0.98)[37].

In the USA five further studies found no association[33,39-43] and two studies report the converse association, increased likelihood of completion with age between 13 and 17 years controlling for year, race, insurance status, this perhaps reflects the perception that it was an 'STI vaccine' in 2007-8[44,45]. No association between age and HPV vaccine completion was found in multivariate analyses in Canada although only one school grade was targeted [33,39-43].

Race

Racial or ethnic identity was analysed in 31 studies from the USA, Australia and Greece; 18 conducted multivariate analyses. Analysis of >100,000 women in North Carolina adjusted for location, clinic, insurance, and age found Black (aOR 0.55; 95%CI 0.53-0.56), American Indian or Alaskan (aOR 0.68; 0.61-0.77) and Hispanic (aOR 0.75; 0.72-0.79) women had 25-45% lower likelihood of completion compared to White women[43]. Race was the only significant predictor of completion in the NIS-Teen household survey in USA[44]. Ten additional large database studies in the USA with multivariate analyses corroborate this association for both HPV and HBV vaccines [15,16,36,37,39,40,42,43,46-48]. However, no association between race and completion was found in 5 studies when controlling for gender, insurance and health clinic characteristics[29,38,45,49,50]. Hispanic adolescents were underrepresented in one survey with a low response rate[29].

Greek non-nationals had lower completion rates (33%) than nationals (60%) for 2 doses of HAV[51]. In the northern territories of Australia, 3 dose coverage of HPV vaccine was lower in indigenous compared to non-indigenous groups (54% vs. 64%), but completion rates were the same (84%)[52].

Insurance

Many countries have supplied HPV vaccine free-of-charge. In the USA, although the vaccine was not initially eligible for reimbursement in some health insurance plans, after it was recommended by the Advisory Committee on Immunization Practices it was included in the Vaccines for Children (VFC) programme which provides for

underinsured and uninsured children[1]. Insurance status was investigated as a risk factor in 25 articles, 16 conducted multivariate analyses (15 USA, 1 France). In 2011, insurance status remained a significant predictor of HPV series completion in the USA; those publicly insured (Medicaid) were 2.08 times (95%CI 1.16-3.7) more likely to complete compared to those with no insurance; those privately insured were not significantly more likely to complete than those on public insurance (aOR 1.16; 95%CI 0.97-1.38) controlling for age, race, contraception use[42]. The association between insurance status and completion was stronger in 2006-8 reflecting policy changes[16,43]. In France completion rates were lower among recipients of complimentary social welfare compared to those with private insurance (aRR 0.88; 95%CI 0.83-0.93)[34].

Longer enrolment on an insurance plan (>12 years) was associated with a 1-14% increase in likelihood of completion of 2 doses of varicella vaccine; 9-12% increased likelihood for HAV and 21-23% for HBV in the vaccine safety database of almost 600,000 people in the USA between 1998-2004[31] controlling for age, gender, healthcare utilisation and provider characteristics.

Across the USA there are substantial differences across states in beliefs, policy, and the rapidity of implementation of changes made at the national level. In Oregon state in 2008, HPV vaccine was offered free of charge and no difference was found in completion rates between publicly and privately insured participants[53]. In Maryland in 2006-10 private insurance was found to be a risk factor for non-completion compared to those publicly insured (aOR 0.76; 95%CI 0.59-0.98), controlling for race and age[37]. No association in multivariate analyses was seen in 5 studies in the USA[29,39,40,44,50].

Gender

Gender was assessed in seven articles; no correlation between completion of HBV and gender was seen in unadjusted results from Greece[51], nor in adjusted results in Australia[35]. In the USA, controlling for delivery site, age, insurance, year, chronic conditions and prior healthcare utilization, male gender was marginally associated with lower completion for varicella (aOR 0.93; 95%CI 0.90-0.96), HAV (aOR 0.98; 0.97-0.99) and HBV (aOR 0.97; 0.96-0.98)[31]. Included studies did not report completion of HPV vaccine in boys, recommendations to vaccinate boys were issues in 2015 in the USA; however, clinics in the USA with higher female:male ratios obtained higher completion rates of HPV vaccine among females (aRR 2.16; 1.13-4.13)[49].

Socio-economic status

Socio-economic status (SES) was analysed in studies in the USA (n=14), Canada (n=2), UK (n=1) and France (n=1); 14 conducted multivariate analysis. Median neighbourhood income and average adult education[54], parental income levels[39,50,55], household income[56] and poverty status[45] were not associated with completion in multivariate analyses.

Every 10,000USD rise in median neighbourhood income was associated with a 15% increase in HBV completion (aRR 1.15; 95%CI 1.06-1.25)[47] and a 1% increased likelihood of HPV completion in 20,000 9-17 year old American girls(aRR 1.01; 1.01-1.02)[57]. Average census block education level was positively associated at a similar magnitude of effect (aRR 1.03; 1.02-1.05)[57]. Adolescent girls living below the federal poverty level were significantly less likely to complete vaccination compared to adolescents with household incomes >$75,000 (aOR 0.76; 0.63-0.92)[44].

The effect of SES may differ by delivery strategy; in Canadian public schools with in-school HPV vaccine delivery, completion increased as SES decreased, in Catholic schools in which the pupils relied on community delivery, completion decreased as SES decreased[58]. A linear trend with the Scottish multiple index of deprivation was found with completion but not with initiation; however, the difference between the most and least deprived groups was small (8%) and disappeared with the administration of a catch-up dose 1 year later[59]. Girls in Canada in 2007-8 living in lower income neighbourhoods were significantly less likely to complete HPV vaccine than girls living in middle income neighbourhoods (aOR 0.45; 0.28-0.72)[33]. In France compliance with the HPV vaccine schedule was lower in social welfare recipients compared to non-recipients (aRR 0.88, 0.83-0.93)[34].

Healthcare utilization

History of health care utilization was inconsistently associated with completion. Seventeen articles from the USA, France and Australia analysed an individual's prior use of health care (defined by receipt of other recommended vaccines, or the number of prior visits to a primary health care provider) and completion of a multi-dose series of varicella, HPV or HBV vaccines. In adjusted analyses in the USA, >10 visits to a health care provider in the last year was associated with 15% increased likelihood of HPV vaccine completion and a 4-6% increase in HBV completion[31]. Similar findings were reported in France where compliance with the HPV vaccine

regimen was 10% higher if a girl had >6 consultations with a family physician in the past year[34]. The magnitude of the effect is supported by reports of a 2% increased likelihood of completing the HPV vaccine series with every primary care provider visit in the past year[36].

A further eight studies found no association between vaccine completion and the number of visits to a primary healthcare in the preceding 2 years[60], non-acute care in the year preceding initiation[29,33,39,44,55], previous prescriptions[47] or receipt of tetanus, diphtheria, and pertussis booster (Tdap) and meningococcal vaccines[38].

Recorded contraceptive use (DMPA) at any time in the medical records by HPV vaccine recipients was associated with a two-fold increase (95%CI 1.72-2.47) in the odds of HPV vaccine completion[42]. In Canada, HBV vaccination conferred 16.9 times higher odds (95%CI 14.8-19.2) for HPV vaccine completion in comparison with those who had not received HBV. However, the association could be confounded by the differing vaccination policies and delivery strategies by school[58]. In Australia in an area with a high risk population, including young sex workers and drug users, a shorter time interval (<2 weeks) between first contact with the health care provider and initiation of vaccine series correlated with better HBV completion[35].

Vaccine related knowledge

Three American studies examined knowledge in relation to completion in multivariate analysis[45,47,55]. The ability to correctly identify the number of required doses remained associated with series completion (aRR 1.38; 95%CI 1.08-1.76)[55]. Parents who remember receiving a provider recommendation for vaccination were more likely to have daughters who completed the regimen (aOR 2.71; 1.99-3.70)[45]. However, general knowledge of HPV and HBV vaccine was not associated with completion in adjusted analyses[45,47].

Adverse events

Three studies assessed whether experience of adverse events following HPV vaccination affected series completion in the USA. Parents of daughters who had completed the three dose series reported pain or discomfort as often as parents whose daughters were late for their second or third dose (OR 0.76; 95%CI 0.33-1.77)[61]. In a survey of over 3000 vaccine recipients[55] (response rate 27%), multivariate analysis controlling for age, socio-economic status, health care

utilization, showed reports of bruising or swelling at first dose did not affect completion of the series (aRR 0.88; 0.7-1.00). An association was not apparent for those reporting pain, syncope or dizziness[55]. A qualitative study of 18 women in the USA who did not complete the HPV vaccine series found none of them mentioned adverse events as a reason[62].

Risk behaviour

A variety of risk behaviours in seven studies were assessed in relation to completion of HBV or HPV vaccine schedules; no associations were found. Drug use, history of sexually transmitted infections (STIs), or alcohol use was not associated with completion in the USA[38,47,63]. In multivariate analysis in Australia, intravenous drug use, sex work, or hepatitis C status did not correlate with likelihood of completion of HPV in a health unit serving at-risk populations[35].

Concomitant healthcare

Three articles assessed the effect of concomitant health service delivery on adherence to HPV in the USA**.** Receipt of another vaccine at the time of HPV vaccination was not associated with odds of HPV completion controlling for socio-demographic and provider characteristics[55]. However, if the first dose was given at a health care provider visit which was attended primarily for another reason other than HPV, the odds of a mistimed 3rd dose were almost double (aOR 1.97; 95%CI 1.39-2.80) than that if the first dose was at a vaccine only visit, controlling for age and race[48]. Type of visit was not associated in analysis investigating the effect of age and healthcare utilization[41].

Access

Access to vaccination sites was assessed in two studies in the USA. Compliance to the schedule and completion of the series were not governed by proximity or mode of transportation to the clinical site[47]. Distance from home to clinic was not associated with completion controlling for age, race, and healthcare utilization[40].

Qualitative studies

One qualitative study investigated why 9-26 year olds did not return for the final dose of the HPV vaccine series, in non-exclusive responses: 33% claimed they didn't know they were meant to obtain further doses, 23% claimed they were too busy,

15% cited inconvenience, 38.5% claimed they were too busy or forgot, 7.7% claimed they were too busy and times were inconvenient[62]. Two additional surveys of partially vaccinated university students in the USA and Australia indicated the potential problems with vaccinating older age groups who have competing priorities, reasons focused on inconvenience and lack of time[64,65].

Maternal characteristics

Three studies in the USA analyzed the relationship between maternal preventative behavior (cervical screening) and their daughter's HPV vaccine series completion. In multivariate analysis, controlling for demographic, socioeconomic, family, and health plan characteristics, all three studies found that girls whose mothers had received a pap smear in the past three years were more likely to complete the HPV vaccine series (aOR 1.07, 95%CI 1.06-1.08)[56]; 1.42, 1.31-1.54[54] and 1.87, 1.31-2.75[66]) .

The relationship between maternal education and vaccine series completion was assessed in eight studies conducted in the USA (n=7) and in Greece[51]. Adolescents whose mothers had less than high school education were less likely to complete the vaccine series in multivariate analysis[44,66]; both studies controlled for adolescent age, SES, and mother's health characteristics and found similar effect estimates (aOR 0.68; 95%CI 0.56-0.84)[44]; aOR 0.60; 0.41-0.87[66]). No association between maternal education and HPV or HAV vaccine series completion in multivariate analysis was found in three studies[39,45,50].

Maternal age and marital status were found to have no or very slight associations with vaccine series completion in four of the five included studies[39,44,45,66]. In unadjusted analysis, one study found daughters with mothers aged over 40 years were more likely to complete the HPV vaccine series compared to mothers who were less than 40 years old[56].

Provider/ Organisational characteristics

Delivery model

There is strong evidence for high completion rates with school-delivery in high income and low-middle income countries. Canadian in-school HPV vaccination completion rates were 75% (95%CI 74.7-75.8) compared to 36% (95%CI 35.3-37.2) for girls provided with a community-delivery model[58]. In-school vaccinations conferred 1.8 times the odds of completing the HBV series compared to if

adolescents had to go off-site (95%CI 1.15-2.8) in a parent survey in the USA controlling for age, race, insurance, SES, prior healthcare utilization[29].

Only 2 articles included data from low and middle-income countries (LAMIC); descriptive results are available regarding the success of different delivery strategies[67]. In Uganda, a school-based strategy appeared more successful (94% completion) than a strategy in which the vaccine was given in the community with a child health programme (79-87% completion year 1-year 2) although the delivery strategies had slightly different target populations. Peru's school-based strategy achieved 98.7% completion, whilst combined school-based and health centre strategies in Vietnam achieved >99% completion. In India, very similar completion rates were achieved in campaign and routine delivery approaches (97-98%)[67]. Differences in completion rates achieved in 21 demonstration projects in 14 countries implementing different models of delivery were insignificant[68]; however, the mixed model (school based delivery with mop-up activities at health centres) seemed to confer marginally higher completion (96.6%), the school-only model was intermediate (88.6%) and the health facility-only model was least effective (79.7%)(p=0.39)[69].

In Australia, high-risk groups, benefited from an accelerated schedule (0, 7, 21 days and 12 months), which increased the likelihood of HBV vaccine completion 1.35 times (1.01-1.80) controlling for drug use, and length of contact with the health facility[35].

Provider characteristics

Vaccine schedule completion was higher in an American school based programme when students returned the consent forms to their teacher compared to the school nurse[70]. In 1994-5 in Canada, initial parental consent was lower at private schools compared to public schools; however, private and public schools did not differ in completion rates. Different education providers (teachers or public health nurses) did not have an effect on completion, although education from teachers was associated with higher consent[30].

A further 17 studies investigated health provider characteristics, of which 12 reported adjusted analyses. There was no evidence that the speciality of an adolescent girl's primary care physician influenced HPV series completion in multivariate analyses[15,16,36,42,49,55]. However, for women >17 years of age in the USA, those with a paediatric/ internal medicine physician were slightly less likely to complete the HPV

regimen than those with a family medicine physician. Female providers were not significantly associated with completion (male primary care provider aRR0.93 0.85-1.01)[36]. In an American datalink study, those vaccinated at paediatric clinics had the highest completion (61%) compared to family care practices (53%; aOR 0.78; 95%CI 0.76-0.80) and the local health departments (39%; aOR 0.48; 0.47-0.50)[43].

Discussion

We present a comprehensive review of the available literature on factors influencing adherence to multi-dose vaccine schedules among adolescents. The majority of studies took place in the USA (n=49), the remainder included Canada (n=3), France (n=3), Australia (n=2), Greece (n=1), the UK (n=1) and 2 multi-country studies including LAMICs. The two studies including LAMICs focused on organisational level factors and reported high adherence to HPV vaccine [68], therefore our summaries of individual level factors are limited in generalizability to developed settings. The high level of variation in the definitions, number and selection of factors investigated in each study limits the comparability of study results and prevented conduct of a meta-analysis. The overall impact of the identified characteristics on vaccine adherence is likely to be dependent on the mix of other factors present, as well as the programmatic and local context.

Good adherence to multi-dose vaccines appears to be higher in early adolescence (9-12 year olds) when compared to later adolescence (>14 years old). It is unclear whether this is linked to adolescent health seeking behaviour, which was inconsistently associated with completion, or whether it is governed by logistical reasons as cited in qualitative results. It could reflect factors which are not explored in the available literature such as which groups were most targeted with communication materials or the general decrease in utilization of health services through adolescence[71]. In some populations in the USA, there is evidence that Black or Hispanic girls are disproportionately prone to low completion rates when compared to White girls after adjustment for socioeconomic status and insurance, despite some reports of similar rates of initiation. Adolescent females may have a slightly elevated likelihood of vaccine completion compared to males; this association may be a symptom of increased opportunity whilst accessing contraception at the health centre. Higher household income, maternal education and maternal preventative health behaviour were associated with higher completion rates when compared to lower socio-economic families and those mothers who rarely sought

screening. Insurance status may have a decreasing effect on completion over time as knowledge spreads that both HBV and HPV vaccines are eligible for reimbursement on any insurance plan in the USA. Experience of adverse events and general knowledge about the vaccine did not affect completion rates. School-based delivery alongside supplying vaccine to health centres for out-of-school girls appears to be a successful approach in countries with relatively high school attendance, including some LAMICs[69], the UK[59] and Canada[58].

Conclusion

The factors that affect rates of vaccine completion are context and time specific. Providers and programme planners should be aware that obtaining good consent and initiation rates is not enough; sub-groups within the population may need more help than others to complete the series. Efforts need to continue past the first dose to reduce inequality in completion. Adolescents captured for the first dose remain only partially protected from vaccine related disease until receipt of the final dose of the schedule.

Opportunistic vaccination at the delivery point of other services should be utilized as a strategy to increase vaccine completion. There is no evidence that concomitant service delivery is associated with lower completion. Among 11-18 year olds in Seattle, 71% of visits to a primary health practitioner in 2006-11 were found to be lost opportunities for dose 3 of HPV vaccine[72]. Especially utilizing visits that were not originally for preventative health care services could rapidly improve completion rates and access those adolescents with low healthcare utilization[71,72].

A Cochrane review in 2005 found 47 articles detailing the effect of patient reminder/recall on vaccine uptake, all were conducted in developed countries, only one study was conducted in adolescents [73]. In pooled results across all age groups, all reminder/recall systems appeared to improve coverage compared to the control groups. Personal telephone reminders were the most effective intervention (OR 1.92; 1.2-3.07). Letter reminders were close to the effectiveness of phone reminders (OR 1.79; 1.5-2.15), postcard alone was less effective (OR 1.44; 1.09-1.89), and automated phone calls were least effective (OR 1.29; 1.09-1.53). Interventions to improve completion of vaccine series need to be assessed and the use of novel technologies needs to be explored where electronic records and recall systems are not available.

Word Count: 4164

Conflicts of Interest: None

Author contributions:

KEG carried out article screening, synthesis and drafted the manuscript

EK carried out article screening and synthesis

LOE carried out article screening

SM carried out article screening

SM-J carried out article screening (French)

MA carried out article screening (Spanish)

DAR provided input on the design and methods

DWJ provided input on the design and methods

All authors read, revised and approved the final manuscript.

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Figure 3.1 Systematic review flow diagram

Caption: The PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened and the full texts retrieved.

**Some articles analysed >1 vaccine*

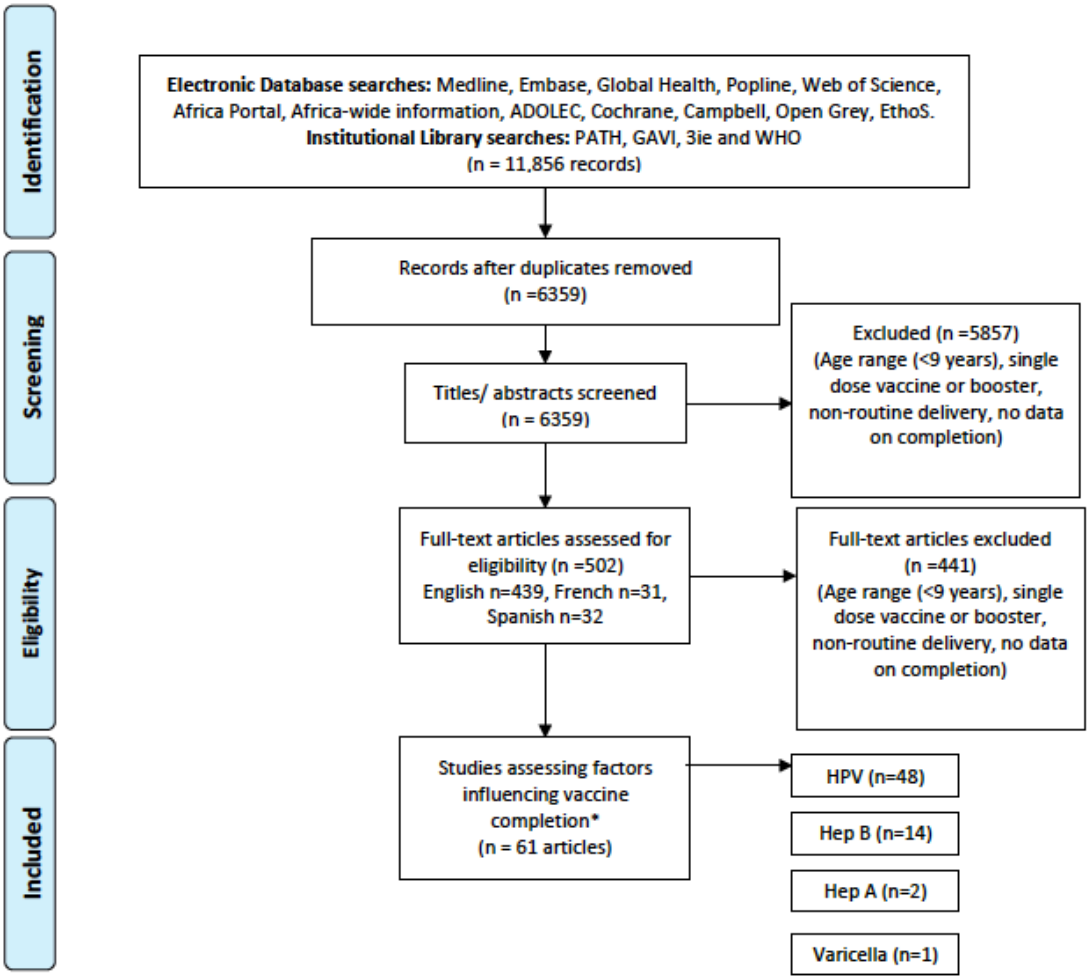

Table 3.1 WHO recommended vaccine schedule for adolescents

Caption: The WHO recommended schedule of vaccines for adolescents (10-19 years of age inclusive), if not given prior to age 10 years[6].

Recommended vaccines for all adolescents	Adolescent dosage	Licensed age
Tetanus, diphtheria, pertussis	3 doses Tdap* & Td Booster	Infant onwards
Human papillomavirus	2 doses if ≤15 years 3 doses thereafter	≥9 years
Meningococcal conjugate	MenA: 1 dose MenC: 1 dose MCV4: 1 dose	Infant onwards
Influenza	1 dose Yearly booster	≥9 years
Hepatitis A	1 dose	Infant onwards
Hepatitis B	3 doses*	Infant onwards
Measles, Mumps, Rubella	1 dose*	Infant onwards
Recommended in at-risk areas	**Adolescent dosage**	**Licensed age**
Tick borne encephalitis	3 doses	Infant onwards
Japanese encephalitis	1 dose	Infant onwards
Typhoid	Vi polysaccharide: 1 dose Ty21a live oral vaccine: 3-4 doses Booster 3-7 years after primary series	Infant onwards
Cholera	Dukoral, Shanchol & mORCVAX: 2 doses booster every 2nd yr	≥2 years
Rabies	3 doses	Infant onwards
Varicella	2 doses	≥9-12 months

*Recommended schedule if not administered prior to age 10 years.

Table 3.2 Study inclusion criteria

Caption: Abstracts and full texts were screened independently by two authors using the following criteria.

Study definitions and characteristics	**Inclusion criteria: Studies investigating factors governing adherence**
Study population	Any child/adolescent 9-19 years old, recruited from the community or a cohort of vaccines, care-givers or care-providers
Geographical setting	No restriction
Vaccine	Any vaccine administered to the study population in a schedule including more than one dose within the same year
Vaccine delivery	Routine vaccine delivery; studies excluded if an outbreak/ campaign setting/ non-routine delivery
Outcome	Completion or non-completion of (or 'adherence to') the intended multi-dose vaccine schedule within 1 year of follow-up
Comparison	Individuals or groups who initiated vaccination (i.e. received dose 1), and completed the vaccine series (i.e. received the final dose) within 1 year, compared to those who initiated the vaccine series but did not receive the final dose within 1 year.
Exposure	Any characteristics of individuals, communities, or programmatic or contextual factors investigated for an association with adherence/completion
Study Design	Any study design with data on and analysis of factors predicting completion of a multi-dose vaccine **in routine settings**
Data	Some estimate of the completion rate achieved must be available

Table 3.3 Summary of included studies by vaccine

Caption: A summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, target age group, delivery strategy, completion rate attained and factors investigated to influence completion, listed by vaccine investigated.

Author; date	Sample size	Country; Source of sample	Year of data collection	Vaccine	Vaccine target age group	Vaccine delivery strategy	Completion rate	Factors investigated to influence completion
Cassidy, W; Mahoney, F. 1995	654	USA. School and administrative data.	1994-5	HBV	School grades 6-8	School-based clinic	82%	Gender, race
Cleves, M. 1998	520	USA. Medical records.	1995-6	HBV	11-19	Available at routine healthcare provider	33%	Age, race, insurance, sexual activity, risk behaviour (drug use)
Deeks, S; Johnson, I. 1998	39,935	Canada. Administrative data from Health units (7), Greater Toronto Area	1994-5	HBV	School Grade 7	School-based delivery	95%	School characteristics, knowledge/ education/mobilisation
Gonzalez, I; et al. 2002	79,357	USA. Electronic Data from 3 Health Management Organisations	1998	HBV	11-12	Available at routine healthcare provider	73%, 67%, 45%	Provider characteristics (Health care organisation)
Lancman, H; et al. 2000	3 centres	USA. Administrative data from 2 school based health centres and one	1997-98	HBV	11 and above	Available at school based health centres and routine	24%, 29%, 76%	Health centre characteristics

		adolescent health clinic				*providers*		
Macdonald, V; et al. 2007	*2471*	*Australia. Health centre records from a primary health care centre, Sydney (high risk population)*	*1992-2003*	*HBV*	*High risk adolescent of any age*	*Available at routine healthcare provider and specialist clinics*	*21%*	*Age, gender, race (aboriginal), risk behaviour (IDU, sex worker, hep.C status) length of contact with the health centre, accelerated versus normal schedule.*
Middleman, A. 2004	*11,500*	*USA. School data*	*1998-2000*	*HBV*	*School grades 5-6*	*School-based*	*72%*	*Insurance, race and gender*
Middleman, A B; et al. 1996	*826*	*USA. Medical records from an adolescent health clinic*	*Unknown*	*HBV*	*Any adolescent attending the clinic*	*Available at routine healthcare provider*	*23%*	*Socio-demographics, risk behaviors (for hepatitis B), medication use, chronic illnesses, and experience, knowledge and attitudes about hepatitis B and the immunization*
Middleman, A B; et al. 1999	*943*	*USA. Questionnaires distributed at hospital and school based clinics*	*1994-5*	*HBV*	*Any adolescent attending the clinics*	*Available at routine healthcare provider and school based clinic*	*47.6% (Clinic); 41.7% (School-based clinic)*	*Race, insurance, residential zip code, risk factors for acquiring hepatitis B, risk behaviors (cigarette and substance use), and academic achievement, chronic illness, healthcare utilization, knowledge about hepatitis B and the vaccination, family history of hepatitis B vaccination,*

								travel time, and mode of transportation to the clinic.
MooreCaldwell, S; et al. 1997	*174*	*USA. Medical records from a university adolescent clinic and junior-senior private high school clinic*	*1992-3*	*HBV*	*Any adolescent attending the clinics*	*Available at routine healthcare provider at school based clinics*	*89%*	*Adolescent and parent knowledge of hepatitis B, perceived risk.*
Seid, M; et al. 2001	*800*	*USA. Survey to parents of children at 5 Schools, San Diego*	*1998*	*HBV*	*11-12*	*Available at routine healthcare provider*	*27%*	*Provider, school based clinics, school socioeconomic status, home language, race, insurance, health care utilization, heard about mandatory vaccination from health care provider.*
Tung, C S; Middleman, A B. 2005	*8918*	*USA, Data from 75 schools participating in HBII (Hep B immunization initiative).*	*1999-2000*	*HBV*	*13-15*	*School-based*	*59%*	*Publicity/promotion, packet distribution, return of forms, ratio of students to clinic, provider characteristics*
Sakou, I I; et al. 2011	*1005*	*Greece. Convenience sample of Adolescent Health Unit attendees*	*2009*	*HBV, HAV, HPV*	*HPV:12-15; HAV, HBV: catch up 11-18*	*Available at routine healthcare provider*	*Not reported*	*Gender, race/ nationality, parental education, family status*

Bednarczyk, R; et al. 2011	*588*	*USA. New York state University health clinics and classrooms: self-report questionnaire .*	*2010*	*HPV*	*11-12 (with catch up to 26)*	*Available at routine healthcare provider*	*79%*	*Qualitative interviews*
Carlos, R; et al. 2010	*232*	*USA. Mailed questionnaire to attendees of breast and cervical cancer screening clinics (maternal report).*	*2010*	*HPV*	*11-12 (with catch up to 26)*	*Available at routine healthcare provider*	*19%*	*Race*
Chao, C; Slezak, J; et al. 2009	*18,275*	*USA. Electronic health records from KPSC managed care organisation.*	*2006-8*	*HPV*	*9-26*	*Available at routine healthcare provider*	*43%*	*Maternal characteristics: history of at least 1 Pap test in the past 3 years, history of abnormal pap test result, history of genital warts/ other STIs, SES (neighbourhood median household income, neighbourhood average adult education)*
Chao, C; Velicer, C; et al. 2009	*34,193*	*USA. Electronic health records from KPSC managed care*	*2006-8*	*HPV*	*9-26*	*Available at routine healthcare provider*	*41%*	*age, race, socioeconomic status (census block neighbourhood statistics, medicaid eligibility), provider characteristics, health care utilization, women's health related*

		organisation.						*conditions, chronic illness*
Chou, B; et al. 2011	*1413*	*USA. Electronic health records from ambulatory care clinics (4) associated with a University.*	*2007-8*	*HPV*	*11-12 (with catch up to 26)*	*Available at routine healthcare provider*	*33%*	*Age, insurance (private/public), provider characteristics (location, practice type (pediatrics, gynaecology or family practice)), race (White, African American, Hispanic).*
Cook, R; et al. 2010	*11,986*	*USA. Medicaid administrative data.*	*2006-8*	*HPV*	*9-20*	*Available at routine healthcare provider*	*27%*	*Age, race, provider of first shot, insurance (months of medicaid enrollment), sexual activity.*
Crosby, R; et al. 2011	*209*	*USA. University of Kentucky, rural community college and rural health clinic attendees*	*2007-8*	*HPV*	*9-26*	*Available at routine healthcare provider*	*56% urban; 10% rural*	*Geography (rural/urban location)*
Dempsey, A; et al. 2010	*2625*	*USA. Health records from 20 university-affiliated health clinics, Michigan*	*2007-8*	*HPV*	*9-26*	*Available at routine healthcare provider*	*15%*	*Age, insurance, race*

Dempsey, A; et al. 2012	*1714*	*USA. Health records from 20 university-affiliated health clinics, Michigan*	*2008-9*	*HPV*	*9-26*	*Available at routine healthcare provider*	*53%*	*Age, insurance, race*
Dorell, C; et al. 2011	*18,228*	*USA. Stratified, national, probability sample of households (NIS-teen survey)*	*2008-10*	*HPV*	*9-26*	*Available at routine healthcare provider*	*53%*	*Age, insurance, health care utilization, household income, maternal education level, maternal age, maternal marital status, race, geography/ location*
Fournier, M; et al. 2013	*1404*	*USA. Electronic medical records from 2 primary care clinics*	*2007-12*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*40%*	*Insurance, race, health care utilization (other vaccines)*
Ganry, O; et al. 2013		*France. Electronic records of the Regime General Insurance (for workers), the RSI (for self-employed) and the RSA (agricultural occupations)*	*2009-10*	*HPV*	*14 (with a catch up to 23; recently revised to 11-14)*	*Available at routine healthcare provider*	*39%*	*Age, insurance, provider characteristics.*
Gold, R; et al. 2013	*786*	*USA. Electronic medical records from*	*2008*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*		*Socioeconomic status; health care utilization; provider characteristics; vaccine delivery*

		an integrated managed care organisation						*concomitant with first dose; experiences at the first visit, challenges to making or keeping the index appointment; Knowledge and attitudes about HPV; adverse events.*
Gold, R; et al. 2011	*450*	*USA. Administrative data from 19 school-based health centres*	*2007-8*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*51%*	*Age, race and insurance status*
Harper, D; et al. 2013	*2422*	*USA. Electronic records from a safety net health care system Kansas*	*2006-09*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*42%*	*Age, race, concomitant (visit type for first dose)*
Hirth, J; et al. 2012	*271,976*	*USA. Electronic records of a private insurance company*	*2006-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*38%*	*Age, provider type, time*
Kester, L; et al. 2011	*500*	*USA. Knowledge networks coordinated survey (nationally representative)*	*2010*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*81%*	*Race, insurance, maternal education, maternal relationship status, maternal history of HPV related condition, geography.*

Kouyoumdjian, F; Bailowitz, A. 2011	*18*	*USA. Baltimore city health department self report interviews*	*2007-9*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*9.80%*	*Geography (access), adverse events, qualitative reasons (convenience, knowledge, pain/discomfort)*
Ladner, J; et al. 2012	*87580*	*Multi-country (7 LAMICs) Administrative data from Gardasil Access Programme grantee countries*	*2009-11*	*HPV*	*Bhutan, Bolivia, Haiti, Nepal: 9-13. Cambodia: 11-18. Cameroon: 9-18. Lesotho: 10-18*	*School based, health centre based or mixed strategies*	*Bhutan: 88%; Bolivia: 96%; Cambodia: 95%; Cameroon 83%, Haiti 76%, Lesotho 93%; Nepal 99%.*	*Delivery strategy (school-based, health facility model, mixed model)*
Laz, T; et al. 2012	*11,277*	*USA. Household questionnaire sent to parents*	*2010*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*49%*	*Age, parental education, insurance, race, parental income.*
Lions, C; et al. 2013	*105,327*	*France. National Insurance Reimbursement database*	*2007-8*	*HPV*	*11-14 (catch up to 19)*	*Available at routine healthcare provider*	*64.10%*	*Age, insurance, geography, medical utilization*
Moore, G; et al. 2010	*209*	*USA. Medical records of community health clinic attendees*	*Unknown*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*28%*	*Attitudes and believes including perceptions of risk, peer experience of HPV vaccine, experience of cancer*

Sinka, K; et al. 2014	*86769*	*UK. The Child Health System database and the Scottish Immunisation Recall System*	*2008-11*	*HPV*	*12-13 (catch up for 13-17)*	*School-based (catch up included supply of vaccine at primary health care)*	*Year 1: 89.4%; Year 2: 86.9%; Year 3: 81%*	*Scottish Index of Multiple Deprivation (SIMD)*
Markovitz, A; et al. 2014	*13,709*	*USA. Immunization registry, Michigan residents continuously enrolled with a PPO*	*2006-11*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*22%*	*Maternal preventive care utilization (Pap testing, mammograms, primary care office visits), age, race, household education, household income, maternal age.*
Monnat, S; Wallington, S. 2013	*4,776*	*USA. Behavioral Risk Factor Surveillance System Survey data in 10 territories*	*2008-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*14%*	*Mother's history of cervical screening (Pap test).*
Moss, J L; et al. 2013	*105,121*	*USA. North Carolina Immunization Registry*	*Not available*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*28%*	*Gender ratio, race, provider specialty and adolescent patient load, reminder/recall system, time to documentation in NCIR, computers per clinic, age of vaccine recommendation (Tdap, Meningococcal, HPV)*

Musto, R; et al. 2013	*35,592*	*Canada. Calgary zone Public Health vaccination database*	*2008-11*	*HPV*	*Grades 5 and 9*	*School-based programme and available at community public health clinics*	*75% (School-based); 36% (community)*	*In-school vs community health clinic delivery model, socioeconomic status, school provider type, history of HBV.*
Neubrand, T; et al. 2009	*352*	*USA. Medical records review from two different sites*	*2007-8*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*58%*	*Age, race, insurance (private vs Medicaid/Child Health Insurance Program [CHIP]), and distance from home to the clinic, sexual activity prior to initiation of the series, history of an STI, cervical screening history within 3 years of vaccine initiation, reason for clinic visit*
Niccolai, L; et al. 2011	*7606*	*USA. NIS-Teen survey: Random digit dialing household survey.*	*2008-9*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*55%*	*Race, socioeconomic status, age, maternal characteristics, insurance, healthcare utilization, geography (region) and year.*
Perkins, R B; et al. 2012	*7702*	*USA. Electronic medical records from Boston Medical/ community health*	*2007-8*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*20%*	*Age, location, number of clinic visits in study period, race, risk behaviour (documentation of STI or alcohol use), history of meningococcal or tdap booster vaccine.*

		centers						
Pruitt, C N; et al. 2013	*978*	*USA. Rochester Epidemiology Project records (REP) from medical records*	*2006-9*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*Somali girls: 52%; white/non-Hispanic: 72%*	*Somali ethnicity*
Rahman, et al. 2013	*2632*	*USA. Data from Behavioral Risk Factor Surveillance System Telephone survey*	*2008-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*17%*	*Geography/ location*
Reiter, P L; et al. 2009	*229*	*USA. Telephone survey, North Carolina.*	*2007-8*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*83%*	*Adverse events/ reported pain from HPV vaccination*
Reiter, P; et al. 2013	*1951*	*USA. NIS-Teen survey: Random digit telephone survey*	*2008-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*28%*	*Age, race, healthcare utilization in last year, insurance, maternal characteristics, knowledge of HPV, provider recommendation, socioeconomic status.*
Rouzier, R; Giordanella, J. 2010	*77,744*	*France. CPAM social security database*	*2007-8*	*HPV*	*14 (Catch up to 23)*	*Available at routine healthcare provider*	*43%*	*Age, provider (general practitioner vs. gynecologist)*

Rubin, R; et al. 2012	*10,821*	*USA, Administrative reimbursement data and medical records from medical group practices*	*2006-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*27%*	*Pre-existing STD, age, provider medical department*
Schluterman, N H; et al. 2011	*8069*	*USA. Database of the University of Maryland Medical Center (UMMC)*	*2006-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*11%*	*Race, insurance status (publicly funded, private, or none), age (9–13, 14–17, or 18–26 years), and place of residence (urban or suburban Baltimore).*
Schmidt, M A; et al. 2013	*311213*	*USA. Administrative data from vaccination sites*	*2006-11*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*42%*	*Age, calendar year*
Schmitt, K; Thompson, D. 2013	*n/a*	*USA. Statewide Immunization Registry*	*2001-11*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*52%*	*Age, insurance, provider type, race*
Smith, L M; et al. 2011	*2519*	*Canada. Universal health insurance program database.*	*2007-10*	*HPV*	*School grade 8*	*School-based*	*86%*	*Age, parental income, and place of residence, vaccination history, health services utilisation, medical history.*
Tan, W; et al. 2011	*138823*	*USA. NCIR immunisation registry*	*2006-2009*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*55%*	*Race, age, county of residence, provider clinic type, insurance.*

Teplow-Phipps, R; et al. 2014	*1,494,767*	*USA. Citywide Immunization Registry (CIR), New York City*	*2005-12*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*38.4% (females); 35.7% (males)*	*Age, gender, insurance, clinic specific variables: provider practice-type, number of Tdap vaccines reported (proxy for practice size), and socioeconomic status of practice location.*
Tracy, J K; et al. 2010	*9658*	*USA. Clinical data repository at the University of Maryland Medical Center*	*2006-10*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*31%*	*Age, race.*
Verdenius, I; et al. 2013	*1563*	*USA. Electronic medical records*	*2006-9*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*32%*	*Age, type of health visit, healthcare utilization, concomitant healthcare delivery.*
Widdice, L E; et al. 2011	*3297*	*USA. Review of medical records from academic medical center*	*2006-8*	*HPV*	*11-12 (catch up to 26)*	*Available at routine healthcare provider*	*28%*	*Age, race, insurance, healthcare utilization (DMPA), clinic location, time period of vaccine series initiation*
LaMontagne, D; et al. 2011	*7269*	*Peru, India, Uganda, Vietnam. Population based household survey*	*2008-10*	*HPV*	*Peru: grade 5; Uganda: grade 5 or age 10; Vietnam: grade 6 or age 11; India: 10-14.*	*School-based or health centre based in all 4 countries*	*Not reported*	*Delivery Strategy*

Nelson, J C; et al; 2009	*590445*	*USA. Vaccine Safety Datalink population (MCO registry)*	*1996-2004*	*Varicella, HAV, HBV*	*9-17*	*Available at routine healthcare provider*	*Varicella: 35.9%; HAV: 48.4% (age 9-12), 40.3% (age 13-17); HBV: 63.4% (age 9-12), 45.1% (age 13-17).*	*Age, provider site, gender, length of MCO enrollment, year of first dose, utilization of medical visits in year prior to dose 1*

Table 3.4 Data available on factors investigated across countries and vaccines

Factor investigated	Countries (Number of studies with multivariate analyses)	Vaccine			
		HPV	HBV	HAV	Varicella
Age	USA (17), Canada (1), France (1), Australia (1)	✓ *			
Race	USA (16), Australia (1), Greece (1)	✓ *	✓ *	✓	
Insurance	USA (15), France (1)	✓ *	✓ *	✓ *	✓ *
Gender	Australia (1), USA (2)		✓ *		✓ *
SES	USA (11), Canada (1), UK (1), France (1)	✓ *	✓ *		
Healthcare utilization	USA (14), France (1), Australia (1), Canada (1)	✓ *	✓ *		✓
Vaccine knowledge	USA (3)	✓	✓		
Adverse events	USA (3)	✓			
Risk behaviour	USA (3), Australia (1)	✓	✓		
Concomitant healthcare	USA (3)	✓			
Access	USA (2)	✓	✓		
Maternal characteristics	Pap smear – USA (3) Education – USA (7), Greece (1)	✓ *		✓	

*Indicates that evidence of a positive association was found in at least one of the multivariate analyses of this factor with vaccine schedule completion.

Supplementary Table 3.1. Search terms and results Medline (Ovid SP)1946 to 2014-02-26.

Caption: An example of the search terms used and the number of hits from Medline database (Ovid SP)

Adolescent vaccine adherence		**Medline(Ovid SP) 1946 to 2013-10-28**	**Results**
Search	**Item**	**Synonyms**	
1	textword	school or young adult$ or youth or boy$ or girl$ or schoolage$ or (school adj1 age$) or schoolchild$ or primary school$ or elementary school$ or prepubescen$ or secondary school$ or pubescen$ or adolescen$ or juvenil$ or teen or teens or teenage$ or (youth or youths) or (highschool$ or (high adj1 school$)) or offspring	2,099,537
2	Subject heading	Exp Adolescent/ Exp adolescent health services/ Exp adolescent medicine/ Exp young adult/	
3	Journal titles	adolescen$.jw. or youth$.jw. or school$.jw.	43,090
4	1 or 2 or 3		2,112,749
4	Textword	Vaccine* or vaccination*or immunis* or immuniz* or human papillomavirus vaccin* or HPV vaccin* or Cervarix or Gardasil or meningococcal vaccin* or Meningitis-A vaccin* or meningococcal-A or MenAfriVac or Meningococcal A+C or POLYSACCHARIDE MENINGOCOCCAL A+C VACCIN* or Hib-MenCY or MCV4-D or MCV4-CRM or Menomune or Meningococcal ACYW-135 Polysaccharide vaccin* or Hepatitis-A vaccin* or HepA vaccin* or Havrix or Hepatitis-B vaccin* or HepB vaccin* or Hep-B vaccin* or Hepatitis-B recombinant or hepatitis-B vaccine recombinant or Euvax B or Engerix-B or Heberbiovac HB or Hepavax-Gene TF or Hepavax-Gene or Shanvac-B	327,567
5	Subject heading	Exp Vaccination/ Exp Immunization programs/ Exp Papillomavirus vaccines/ Meningococcal Vaccines/ Exp viral hepatitis vaccines/	66,191
6	4 or 5		324,475
7	Textword	Coverage or uptake or continuation or completion or adherence or compliance or dropout*or drop-out* or retention	586,046
8	Subject heading	Exp patient compliance/	55,248
9	7 or 8		701,239
10	3 and 6 and 9		**4,762**

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Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review

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Abstract

Background: Completion of multiple dose vaccine schedules is crucial to ensure a protective immune response, and maximise vaccine cost-effectiveness. While barriers and facilitators to vaccine uptake have recently been reviewed, there is no comprehensive review of factors influencing subsequent adherence or completion, which is key to achieving vaccine effectiveness. This study identifies and summarises the literature on factors affecting completion of multi-dose vaccine schedules by adolescents.

Methods: Ten online databases and four websites were searched (February 2014). Studies with analysis of factors predicting completion of multi-dose vaccines were included. Study participants within 9–19 years of age were included in the review. The defined outcome was completion of the vaccine series within 1 year among those who received the first dose.

Results: Overall, 6159 abstracts were screened, and 502 full texts were reviewed. Sixty one studies were eligible for this review. All except two were set in high-income countries. Included studies evaluated human papillomavirus vaccine, hepatitis A, hepatitis B, and varicella vaccines. Reported vaccine completion rates, among those who initiated vaccination, ranged from 27 % to over 90 %. Minority racial or ethnic groups and inadequate health insurance coverage were risk factors for low completion, irrespective of initiation rates. Parental healthcare seeking behaviour was positively associated with completion. Vaccine delivery in schools was associated with higher completion than delivery in the community or health facilities. Gender, prior healthcare use and socio-economic status rarely remained significant risks or protective factors in multivariate analysis.

Conclusions: Almost all studies investigating factors affecting completion have been carried out in developed countries and investigate a limited range of variables. Increased understanding of barriers to completion in adolescents will be invaluable to future new vaccine introductions and the further development of an adolescent health platform.
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Keywords: Vaccines and immunization, Immunization programmes, Vaccination completion, Barriers, Adolescent health services

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Background

In the past decade there has been an increase in the number of new vaccines licensed worldwide [1, 2] and in the accessible funding for vaccine introduction to low-resource settings through the founding of Gavi, The Vaccine Alliance, in 2000 [3]. Multi-dose vaccines in the WHO recommended immunization schedule for adolescents are listed in Table 1; WHO defines adolescence as age 10–19 years inclusive. National vaccine schedules can depart from WHO recommendations, e.g. 2 doses of hepatitis A and meningococcal conjugate vaccines (MCV4) are offered to adolescents in the USA [4]. Although recommended for administration at birth, hepatitis B vaccine (HBV) is routinely offered to older children and adolescents if not previously immunised [5]. In settings where varicella is seen as a public health priority WHO recommends 2 doses of varicella vaccine, with the first dose at 12–18 months and up to 4 month interval between doses [6, 7]. The most recently licensed multi-dose vaccines are the human papillomavirus (HPV) vaccines. In 2014, HPV vaccine recommendations were revised by WHO SAGE from a schedule of 3 doses [8], to 2 doses at a 6 month interval in girls less than or equal to 15 years of age [9, 10] based on evidence of non-inferior immunogenicity [11, 12].

At present, evidence suggests multiple doses of HBV, HPV, and varicella vaccines are needed for efficacious protection against disease in adolescents [5, 9, 13, 14]. However; completion of the vaccine dose series, defined as receipt of the final dose within 1 year of the first dose, has proven challenging in some settings. Completion rates of HPV vaccine were lower than 30 % in the first years of introduction in the USA [15, 16]. Addressing specific difficulties in administering vaccines to adolescents will be invaluable for implementation of future adolescent vaccines and further developing adolescent health services.

The currently available reviews of factors influencing completion focus solely on selected developed countries [1, 17–19], have non-systematic searches [20, 21] or need updating [22]. This systematic review describes factors which have been investigated for their effect on multi-dose vaccine adherence in adolescents to aid development of interventions to improve adherence.

Methods

Search strategy

A comprehensive set of search terms was built around: 1) childhood/adolescence; 2) vaccination/immunisation; 3) adherence/completion. Articles with at least one term

Table 1 WHO recommended vaccine schedule for adolescents[a, b]. Caption: the WHO recommended schedule of vaccines for adolescents (10–19 years of age inclusive), if not given prior to age 10 years

Recommended vaccines for all adolescents	Adolescent dosage	Licensed age
Tetanus, diphtheria, pertussis	3 doses Tdap[a] & Td Booster	Infant onwards
Human papillomavirus	2 doses if ≤15 years	≥9 years
	3 doses thereafter	
Meningococcal conjugate	MenA: 1 dose	Infant onwards
	MenC: 1 dose	
	MCV4: 1 dose	
Influenza	1 dose Yearly booster	≥9 years
Hepatitis A	1 dose	Infant onwards
Hepatitis B	3 doses[a]	Infant onwards
Measles, Mumps, Rubella	1 dose[a]	Infant onwards
Recommended in at-risk areas	**Adolescent dosage**	**Licensed age**
Tick borne encephalitis	3 doses	Infant onwards
Japanese encephalitis	1 dose	Infant onwards
Typhoid	Vi polysaccharide: 1 dose	Infant onwards
	Ty21a live oral vaccine: 3–4 doses	
	Booster 3–7 years after primary series	
Cholera	Dukoral, Shanchol & mORCVAX: 2 doses booster every 2nd yr	≥2 years
Rabies	3 doses	Infant onwards
Varicella	2 doses	≥9–12 months

[a]Recommended schedule if not administered prior to age 10 years
[b]World Health Organization. WHO recommendations for routine immunization - summary tables - http://www.who.int/immunization/policy/immunization_tables/en/ 2014

from each topic were identified. Search terms were informed by the Cochrane Child Health Group recommended terms for adolescents or school children [23] and included international spelling variations (Additional file 1: Table S1). Multi-dose vaccines administered to adolescents were identified through the Centers for Disease, Control, and Prevention (CDC) [6, 24], and the WHO list of prequalified vaccines [25]; however, search terms were not limited to these vaccines.

Medline, Embase, Global Health (Ovid SP), Popline, Web of Science, Africa Portal, Africa-wide information, ADOLEC, Cochrane, Open Grey databases, and PATH, Gavi, and WHO websites were searched in February 2014. No publication date restriction was set. Publications, abstracts and conference proceeding were eligible for inclusion. All texts were collated and reviewed using Endnote X7 (Thompson Reuters); automated and manual de-duplication was performed.

Inclusion criteria

Inclusion criteria for consideration of studies were outlined in a protocol a-priori as per PRISMA guidelines [26] (Table 2). The title and/or abstract of each article were reviewed in the first instance by a single reviewer (KG). Modelling studies, immunogenicity/efficacy trials were excluded. Two reviewers (KG, SM/EK) screened the abstracts. Any study including a vaccine for which more than one dose was administered to persons 9–19 years old in a routine setting within 1 year was considered for inclusion. The WHO definition of adolescent (10–19 years old) was widened to include 9 year olds to include all participants in HPV vaccine studies (WHO recommended for 9–13 year olds). Inclusion criteria were independently applied to full texts by 2 authors (KG, SM/EK) (Fig. 1) [26].

Data extraction

Data were extracted by 2 authors (KG, EK) into separate forms on Microsoft Excel 2010. Article selection and data extraction discrepancies were resolved through discussion. Data on the study population, setting, vaccine, rates of completion and the factors investigated were extracted alongside descriptive, univariate and multivariate results, as applicable.

Assessment of bias

An assessment of bias was recorded on the data extraction form for each study using criteria outlined in the Cochrane tool for assessment of bias in intervention and epidemiological studies [27]. Selection bias and information bias were assessed alongside the potential for confounding.

Data synthesis

Heterogeneity in study methods, population, context and classification of exposure variables, led to a descriptive synthesis. Groups which initiated and completed the recommended vaccine schedule within 1 year were compared to non-completers who only initiated.

Results

Of the 502 full texts reviewed (Fig. 1), 61 articles were eligible for inclusion (Table 3). Included articles reported completion rates for HPV (3-dose completion ranged from 27 % [15] to over 90 % [28]), HBV (27 % completion before a school mandate was introduced in California [29] to 95 % in a school-based programme in Canada [30]),

Table 2 Study inclusion criteria. Caption: abstracts and full texts were screened independently by two authors using the following criteria

Study definitions and characteristics	Inclusion criteria: studies investigating factors governing adherence
Study population	Any child/adolescent 9–19 years old, recruited from the community or a cohort of vaccinees, care-givers or care-providers
Geographical setting	No restriction
Vaccine	Any vaccine administered to the study population in a schedule including more than one dose within the same year
Vaccine delivery	Routine vaccine delivery; studies excluded if an outbreak/campaign setting/non-routine delivery
Outcome	Completion or non-completion of (or 'adherence to') the intended multi-dose vaccine schedule within 1 year of follow-up
Comparison	Individuals or groups who initiated vaccination (i.e. received dose 1), and completed the vaccine series (i.e. received the final dose) within 1 year, compared to those who initiated the vaccine series but did not receive the final dose within 1 year.
Exposure	Any characteristics of individuals, communities, or programmatic or contextual factors investigated for an association with adherence/completion
Study design	Any study design with data on and analysis of factors predicting completion of a multi-dose vaccine in routine settings
Data	Some estimate of the completion rate achieved must be available

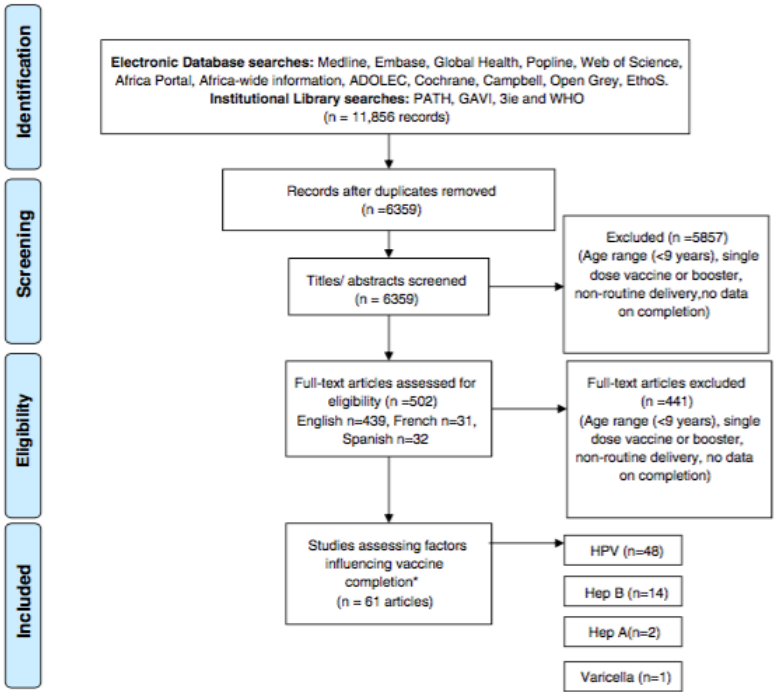

Fig. 1 Systematic review flow diagram. Caption: the PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened and the full texts retrieved. *Some articles analysed >1 vaccine

varicella and hepatitis A vaccine (HAV). In the USA, the two dose series of varicella vaccine was completed within 1 year in 35.9 % of adolescents and 2 doses of HAV were completed in 40–48 % [31]. Searches returned no articles on completion of conjugate meningococcal vaccine, despite a multi-dose policy in the USA [32]. For the purposes of this review we have focused on results from multivariate analyses or qualitative findings. Data availability by country and vaccine is displayed in Table 4.

Individual level factors

Age

The association between age and completion was investigated in 31 articles. Multivariate analyses of at least 2 age categories within the age range of 9–19 years were conducted in 20 studies, in the USA ($n = 17$), Canada [33], France [34], and Australia [35]. Age recommendations vary across countries; results must be interpreted in context.

There is some evidence that completion rates decrease as age of vaccine initiation increases for HPV vaccine, HAV, and HBV [15, 31, 36–38]. In the USA, the HPV vaccine recommended age range is between 11 and 26 years; five studies state similar results among Medicaid enrolees, adjusting for insurance, race, region and year, 17 year olds were 0.84 times less likely to complete HPV vaccine compared to 11 year olds (95 % CI 0.74–0.95) [15]. Among attendees of an urban hospital, in adjusted analyses, 14–17 year olds had 0.71 the odds of completion HPV vaccine when compared to 9–13 years olds (95 % CI 0.59–0.98) [37].

In the USA five further studies found no association [33, 39–43] and two studies report the converse association, increased likelihood of completion with age between 13 and 17 years controlling for year, race, insurance status; this perhaps reflects the perception that it was an 'STI vaccine' in 2007–8 [44, 45]. No association between age and HPV vaccine completion was found in multivariate analyses in Canada although only one school grade was targeted [33, 39–43].

Race

Racial or ethnic identity was analysed in 31 studies from the USA, Australia and Greece; 18 conducted multivariate analyses. Analysis of >100,000 women in North Carolina adjusted for location, clinic, insurance, and age found Black (aOR 0.55; 95 % CI 0.53–0.56), American Indian or Alaskan (aOR 0.68; 0.61–0.77) and Hispanic

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion

Author; date	Sample size	Country; source of sample	Year of data collection	Vaccine	Vaccine target age group	Vaccine delivery strategy	Completion rate	Factors investigated to influence completion
Bednarczyk, R; et al. 2011	588	USA. New York state University health clinics and classrooms: self-report questionnaire.	2010	HPV	11–12 (with catch up to 26)	Available at routine healthcare provider	79 %	Qualitative interviews
Carlos, R; et al. 2010	232	USA. Mailed questionnaire to attendees of breast and cervical cancer screening clinics (maternal report).	2010	HPV	11–12 (with catch up to 26)	Available at routine healthcare provider	19 %	Race
Cassidy, W; Mahoney, F. 1995	654	USA. School and administrative data.	1994-5	HBV	School grades 6–8	School-based clinic	82 %	Gender, race
Chao, C; Slezak, J; et al. 2009	18,275	USA. Electronic health records from KPSC managed care organisation.	2006-8	HPV	9–26	Available at routine healthcare provider	43 %	Maternal characteristics: history of at least 1 Pap test in the past 3 years, history of abnormal pap test result, history of genital warts/ other STIs, SES (neighbourhood median household income, neighbourhood average adult education)
Chao, C; Velicer, C; et al. 2009	34,193	USA. Electronic health records from KPSC managed care organisation.	2006-8	HPV	9–26	Available at routine healthcare provider	41 %	age, race, socioeconomic status (census block neighbourhood statistics, medicaid eligibility), provider characteristics, health care utilization, women's health related conditions, chronic illness
Chou, B; et al. 2011	1413	USA. Electronic health records from ambulatory care clinics (4) associated with a University.	2007-8	HPV	11–12 (with catch up to 26)	Available at routine healthcare provider	33 %	Age, insurance (private/public), provider characteristics (location, practice type (pediatrics, gynaecology or family practice)), race (White, African American, Hispanic).
Cleves, M. 1998	520	USA. Medical records.	1995-6	HBV	11–19	Available at routine healthcare provider	33 %	Age, race, insurance, sexual activity, risk behaviour (drug use)
Cook, R; et al. 2010	11,986	USA. Medicaid administrative data.	2006-8	HPV	9–20	Available at routine healthcare provider	27 %	Age, race, provider of first shot, insurance (months of medicaid enrollment), sexual activity.

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Crosby, R; et al. 2011	209	USA. University of Kentucky, rural community college and rural health clinic attendees	2007-8	HPV	9–26	Available at routine healthcare provider	56 % urban 10 % rural	Geography (rural/urban location)
Deeks, S; Johnson, I. 1998	39,935	Canada. Administrative data from Health units (7), Greater Toronto Area	1994-5	HBV	School Grade 7	School-based delivery	95 %	School characteristics, knowledge/ education/ mobilisation
Dempsey, A; et al. 2010	2625	USA. Health records from 20 university-affiliated health clinics, Michigan	2007-8	HPV	9–26	Available at routine healthcare provider	15 %	Age, insurance, race
Dempsey, A; et al. 2012	1714	USA. Health records from 20 university-affiliated health clinics, Michigan	2008-9	HPV	9–26	Available at routine healthcare provider	53 %	Age, insurance, race
Dorell, C; et al. 2011	18,228	USA. Stratified, national, probability sample of households (NIS-teen survey)	2008-10	HPV	9–26	Available at routine healthcare provider	53 %	Age, insurance, health care utilization, household income, maternal education level, maternal age, maternal marital status, race, geography/ location
Fournier, M; et al. 2013	1404	USA. Electronic medical records from 2 primary care clinics	2007-12	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	40 %	Insurance, race, health care utilization (other vaccines)
Ganry, O; et al. 2013		France. Electronic records of the Regime General Insurance (for workers), the RSI (for self-employed) and the RSA (agricultural occupations)	2009-10	HPV	14 (with a catch up to 23) (recently revised to 11–14)	Available at routine healthcare provider	39 %	Age, insurance, provider characteristics.
Gold, R; et al. 2013	786	USA. Electronic medical records from an integrated managed care organisation	2008	HPV	11–12 (catch up to 26)	Available at routine healthcare provider		Socioeconomic status; health care utilization; provider characteristics; vaccine delivery concomitant with first dose; experiences at the first visit, challenges to making or keeping the index appointment; Knowledge and attitudes about HPV; adverse events.
Gold, R; et al. 2011	450	USA. Administrative data from 19 school-based health centres	2007-8	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	51 %	Age, race and insurance status
Gonzalez, I; et al. 2002	79,357	USA. Electronic Data from 3 Health Management Organisations	1998	HBV	11–12	Available at routine healthcare provider	73 %, 67 %, 45 %	Provider characteristics (Health care organisation)

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Harper, D; et al. 2013	2422	USA. Electronic records from a safety net health care system Kansas	2006-09	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	42 %	Age, race, concomitant (visit type for first dose)
Hirth, J; et al. 2012	271,976	USA. Electronic records of a private insurance company	2006-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	38 %	Age, provider type, time
Kester, L; et al. 2011	500	USA. Knowledge networks coordinated survey (nationally representative)	2010	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	81 %	Race, insurance, maternal education, maternal relationship status, maternal history of HPV related condition, geography.
Kouyoumdjian, F; Bailowitz, A. 2011	18	USA. Baltimore city health department self report interviews	2007-9	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	9.80 %	Geography (access), adverse events, qualitative reasons (convenience, knowledge, pain/discomfort)
Ladner, J; et al. 2012	87580	Multi-country (7 low resource countries). Administrative data from Gardasil Access Programme grantee countries	2009-11	HPV	Bhutan, Bolivia, Haiti, Nepal: 9–13 Cambodia: 11–18 Cameroon: 9–18 Lesotho: 10–18	School based, health centre based or mixed strategies	Bhutan: 88 %, Bolivia: 96 %; Cambodia: 95 %; Cameroon 83 %, Haiti 76 %, Lesotho 93 %; Nepal 99 %.	Delivery strategy (school-based, health facility model, mixed model)
Lancman, H; et al. 2000	3 centres	USA. Administrative data from 2 school based health centres and one adolescent health clinic	1997-98	HBV	11 and above	Available at school based health centres and routine providers	24 %, 29 %, 76 %	Health centre characteristics
Laz, T; et al. 2012	11,277	USA. Household questionnaire sent to parents	2010	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	49 %	Age, parental education, insurance, race, parental income.
Lions, C; et al. 2013	105,327	France. National Insurance Reimbursement database	2007-8	HPV	11–14 (catch up to 19)	Available at routine healthcare provider	64.10 %	Age, insurance, geography, medical utilization
Macdonald, V; et al. 2007	2471	Australia. Health centre records from a primary health care centre, Sydney (high risk population)	1992-2003	HBV	High risk adolescent of any age	Available at routine healthcare provider and specialist clinics	21 %	Age, gender, race (aboriginal), risk behaviour (IDU, sex worker, hep.C status) length of contact with the health centre, accelerated versus normal schedule.
Moore, G; et al. 2010	209	USA. Medical records of community health clinic attendees	Unknown	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	28 %	Attitudes and believes including perceptions of risk, peer experience of HPV vaccine, experience of cancer

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Nelson, J C; et al; 2009	590445	USA. Vaccine Safety Datalink population (MCO registry)	1996-2004	Varicella, HAV, HBV	9–17	Available at routine healthcare provider	Varicella: 35.9 %; HAV: 48.4 % (age 9–12), 40.3 % (age 13–17); HBV: 63.4 % (age 9–12), 45.1 % (age 13–17).	Age, provider site, gender, length of MCO enrollment, year of first dose, utilization of medical visits in year prior to dose 1
Sinka, K; et al. 2014	86769	UK. The Child Health System database and the Scottish Immunisation Recall System	2008-11	HPV	12–13 (catch up for 13–17)	School-based (catch up included supply of vaccine at primary health care)	Year 1: 89.4 % Year 2: 86.9 % Year 3: 81 %	Scottish Index of Multiple Deprivation (SIMD)
Markovitz, A; et al. 2014	13,709	USA. Immunization registry, Michigan residents continuously enrolled with a PPO	2006-11	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	22 %	Maternal preventive care utilization (Pap testing, mammograms, primary care office visits), age, race, household education, household income, maternal age.
Middleman, A. 2004	11,500	USA. School data	1998-2000	HBV	School grades 5–6	School-based	72 %	Insurance, race and gender
Middleman, A B; et al. 1996	826	USA. Medical records from an adolescent health clinic	Unknown	HBV	Any adolescent attending the clinic	Available at routine healthcare provider	23 %	Socio-demographics, risk behaviors (for hepatitis B), medication use, chronic illnesses, and experience, knowledge and attitudes about hepatitis B and the immunization
Middleman, A B; et al. 1999	943	USA. Questionnaires distributed at hospital and school based clinics	1994-5	HBV	Any adolescent attending the clinics	Available at routine healthcare provider and school based clinic	47.6 % (Clinic); 41.7 % (School-based clinic)	Race, insurance, residential zip code, risk factors for acquiring hepatitis B, risk behaviors (cigarette and substance use), and academic achievement, chronic illness, healthcare utilization, knowledge about hepatitis B and the vaccination, family history of hepatitis B vaccination, travel time, and mode of transportation to the clinic.
Monnat, S; Wallington, S. 2013	4,776	USA. Behavioral Risk Factor Surveillance System Survey data in 10 territories	2008-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	14 %	Mother's history of cervical screening (Pap test).
MooreCaldwell, S; et al. 1997	174	USA. Medical records from a university adolescent clinic and junior-senior private high school clinic	1992-3	HBV	Any adolescent attending the clinics	Available at routine healthcare provider at school based clinics	89 %	Adolescent and parent knowledge of hepatitis B, perceived risk.

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Moss, J L; et al. 2013	105,121	USA. North Carolina Immunization Registry	Not available	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	28 %	Gender ratio, race, provider specialty and adolescent patient load, reminder/ recall system, time to documentation in NCIR, computers per clinic, age of vaccine recommendation (Tdap, Meningococcal, HPV)
Musto, R; et al. 2013	35,592	Canada. Calgary zone Public Health vaccination database	2008-11	HPV	Grades 5 and 9	School-based programme and available at community public health clinics	75 % (School-based); 36 % (community)	In-school vs community health clinic delivery model, socioeconomic status, school provider type, history of HBV.
Neubrand, T; et al. 2009	352	USA. Medical records review from two different sites	2007-8	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	58 %	Age, race, insurance (private vs Medicaid/Child Health Insurance Program (CHIP)), and distance from home to the clinic, sexual activity prior to initiation of the series, history of an STI, cervical screening history within 3 years of vaccine initiation, reason for clinic visit
Niccolai, L; et al. 2011	7606	USA. NIS-Teen survey: Random digit dialing household survey.	2008-9	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	55 %	Race, socioeconomic status, age, maternal characteristics, insurance, healthcare utilization, geography (region) and year.
Perkins, R B; et al. 2012	7702	USA. Electronic medical records from Boston Medical/ community health centers	2007-8	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	20 %	Age, location, number of clinic visits in study period, race, risk behaviour (documentation of STI or alcohol use), history of meningococcal or tdap booster vaccine.
Pruitt, C N; et al. 2013	978	USA. Rochester Epidemiology Project records (REP) from medical records	2006-9	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	Somali girls: 52 %; white/non-Hispanic: 72 %	Somali ethnicity
Rahman, et al. 2013	2632	USA. Data from Behavioral Risk Factor Surveillance System Telephone survey	2008-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	17 %	Geography/ location
Reiter, P L; et al. 2009	229	USA. Telephone survey, North Carolina.	2007-8	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	83 %	Adverse events/ reported pain from HPV vaccination

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Reiter, P; et al. 2013	1951	USA. NIS-Teen survey: Random digit telephone survey	2008-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	28 %	Age, race, healthcare utilization in last year, insurance, maternal characteristics, knowledge of HPV, provider recommendation, socioeconomic status.
Rouzier, R; Giordanella, J. 2010	77,744	France. CPAM social security database	2007-8	HPV	14 (Catch up to 23)	Available at routine healthcare provider	43 %	Age, provider (general practitioner vs. gynecologist)
Rubin, R; et al. 2012	10,821	USA. Administrative reimbursement data and medical records from medical group practices	2006-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	27 %	Pre-existing STD, age, provider medical department
Sakou, I I; et al. 2011	1005	Greece. Convenience sample of Adolescent Health Unit attendees	2009	HBV, HAV, HPV	HPV: 12–15; HAV, HBV: catch up 11–18	Available at routine healthcare provider	Not reported	Gender, race/ nationality, parental education, family status
Schluterman, N H; et al. 2011	8069	USA. Database of the University of Maryland Medical Center (UMMC)	2006-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	11 %	Race, insurance status (publicly funded, private, or none), age (9–13, 14–17, or 18–26 years), and place of residence (urban or suburban Baltimore).
Schmidt, M A; et al. 2013	311213	USA. Administrative data from vaccination sites	2006-11	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	42 %	Age, calendar year
Schmitt, K; Thompson, D. 2013	n/a	USA. Statewide Immunization Registry	2001-11	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	52 %	Age, insurance, provider type, race
Seid, M; et al. 2001	800	USA. Survey to parents of children at 5 Schools, San Diego	1998	HBV	11–12	Available at routine healthcare provider	27 %	Provider, school based clinics, school socioeconomic status, home language, race, insurance, health care utilization, heard about mandatory vaccination from health care provider.
Smith, L M; et al. 2011	2519	Canada. Universal health insurance program database.	2007-10	HPV	School grade 8	School-based	86 %	Age, parental income, and place of residence, vaccination history, health services utilisation, medical history.
Tan, W; et al. 2011	138823	USA. NCIR immunisation registry	2006-2009	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	55 %	Race, age, county of residence, provider clinic type, insurance.

Table 3 Summary of included studies. Caption: a summary of the studies included in the review, including details of sample size, the source of the sample, year of data collection, vaccine investigated, target age group, delivery strategy, completion rate attained and factors investigated to influence completion *(Continued)*

Teplow-Phipps, R; et al. 2014	1,494767	USA. Citywide Immunization Registry (CIR), New York City	2005-12	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	38.4 % (females) 35.7 % (males)	Age, gender, insurance, clinic specific variables: provider practice-type, number of Tdap vaccines reported (proxy for practice size), and socioeconomic status of practice location.
Tracy, J K; et al. 2010	9658	USA. Clinical data repository at the University of Maryland Medical Center	2006-10	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	31 %	Age, race.
Tung, C S; Middleman, A B. 2005	8918	USA, Data from 75 schools participating in HBII (Hep B immunization initiative).	1999-2000	HBV	13–15	School-based	59 %	Publicity/promotion, packet distribution, return of forms, ratio of students to clinic, provider characteristics
Verdenius, I; et al. 2013	1563	USA. Electronic medical records	2006-9	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	32 %	Age, type of health visit, healthcare utilization, concomitant healthcare delivery.
Widdice, L E; et al. 2011	3297	USA. Review of medical records from academic medical center	2006-8	HPV	11–12 (catch up to 26)	Available at routine healthcare provider	28 %	Age, race, insurance, healthcare utilization (DMPA), clinic location, time period o f vaccine series initiation
LaMontagne, D; et al. 2011	7269	Peru, India, Uganda, Vietnam. Population based household survey	2008-10	HPV	Peru: grade 5; Uganda: grade 5 or age 10; Vietnam: grade 6 or age 11; India: 10–14.	School-based or health centre based in all 4 countries	Not reported	Delivery Strategy

Table 4 Data available on factors investigated across countries and vaccines

Factor investigated	Countries (Number of studies with multivariate analyses)	Vaccine			
		HPV	HBV	HAV	Varicella
Age	USA (17), Canada (1), France (1), Australia (1)	✓			
Race	USA (16), Australia (1), Greece (1)	✓	✓	✓	
Insurance	USA (15), France (1)	✓	✓	✓	✓
Gender	Australia (1), USA (2)		✓		✓
Socio-economic status	USA (11), Canada (1), UK (1), France (1)	✓	✓		
Healthcare utilization	USA (14), France (1), Australia (1), Canada (1)	✓	✓		✓
Vaccine knowledge	USA (3)	✓	✓		
Adverse events	USA (3)	✓			
Risk behaviour	USA (3), Australia (1)	✓	✓		
Concomitant healthcare	USA (3)	✓			
Access	USA (2)	✓	✓		
Maternal characteristics	Pap smear history – USA (3)	✓		✓	
	Education – USA (7), Greece (1)				

(aOR 0.75; 0.72–0.79) women had 25–45 % lower likelihood of completion compared to White women [43]. Race was the only significant predictor of completion in the NIS-Teen household survey in USA [44]. Ten additional large database studies in the USA with multivariate analyses corroborate this association for both HPV and HBV vaccines [15, 16, 36, 37, 39, 40, 42, 43, 46–48]. However, no association between race and completion was found in 5 studies when controlling for gender, insurance and health clinic characteristics [29, 38, 45, 49, 50]. Hispanic adolescents were underrepresented in one survey with a low response rate [29].

Greek non-nationals had lower completion rates (33 %) than nationals (60 %) for 2 doses of HAV [51]. In the northern territories of Australia, 3 dose coverage of HPV vaccine was lower in indigenous compared to non-indigenous groups (54 % vs. 64 %), but completion rates were the same (84 %) [52].

Insurance

Many countries have supplied HPV vaccine free-of-charge. In the USA, although the vaccine was not initially eligible for reimbursement in some health insurance plans, after it was recommended by the Advisory Committee on Immunization Practices it was included in the Vaccines for Children (VFC) programme which provides for under-insured and uninsured children [1]. Insurance status was investigated as a risk factor in 25 articles, 16 conducted multivariate analyses (15 USA, 1 France). In 2011, insurance status remained a significant predictor of HPV series completion in the USA; those publicly insured (Medicaid) were 2.08 times (95 % CI 1.16–3.7) more likely to complete compared to those with no insurance; those privately insured were not significantly more likely to complete than those on public insurance (aOR 1.16; 95 % CI 0.97–1.38) controlling for age, race, contraception use [42]. The association between insurance status and completion was stronger in 2006–8 reflecting policy changes [16, 43]. In France completion rates were lower among recipients of complimentary social welfare compared to those with private insurance (aRR 0.88; 95 % CI 0.83–0.93) [34].

Longer enrolment on an insurance plan (>12 years) was associated with a 1–14 % increase in likelihood of completion of 2 doses of varicella vaccine; 9–12 % increased likelihood for HAV and 21–23 % for HBV in the vaccine safety database of almost 600,000 people in the USA between 1998 and 2004 [31] controlling for age, gender, healthcare utilisation and provider characteristics.

Across the USA there are substantial differences across states in beliefs, policy, and the rapidity of implementation of changes made at the national level. In Oregon state in 2008, HPV vaccine was offered free of charge and no difference was found in completion rates between publicly and privately insured participants [53]. In Maryland in 2006–10 private insurance was found to be a risk factor for non-completion compared to those publicly insured (aOR 0.76; 95 % CI 0.59–0.98), controlling for race and age [37]. No association in multivariate analyses was seen in 5 studies in the USA [29, 39, 40, 44, 50].

Gender

Gender was assessed in seven articles; no correlation between completion of HBV and gender was seen in unadjusted results from Greece [51], nor in adjusted results in Australia [35]. In the USA, controlling for delivery site, age, insurance, year, chronic conditions and

prior healthcare utilization, male gender was marginally associated with lower completion for varicella (aOR 0.93; 95 % CI 0.90–0.96), HAV (aOR 0.98; 0.97–0.99) and HBV (aOR 0.97; 0.96–0.98) [31]. Included studies did not report completion of HPV vaccine in boys, recommendations to vaccinate boys were issued in 2015 in the USA; however, clinics in the USA with higher female:male ratios obtained higher completion rates of HPV vaccine among females (aRR 2.16; 1.13–4.13) [49].

Socio-economic status

Socio-economic status (SES) was analysed in studies in the USA ($n = 14$), Canada ($n = 2$), UK ($n = 1$) and France ($n = 1$); 14 conducted multivariate analysis. Median neighbourhood income and average adult education [54], parental income levels [39, 50, 55], household income [56] and poverty status [45] were not associated with completion in multivariate analyses.

Every 10,000USD rise in median neighbourhood income was associated with a 15 % increase in HBV completion (aRR 1.15; 95 % CI 1.06–1.25) [47] and a 1 % increased likelihood of HPV completion in 20,000 9–17 year old American girls (aRR 1.01; 1.01–1.02) [57]. Average census block education level was positively associated at a similar magnitude of effect (aRR 1.03; 1.02–1.05) [57]. Adolescent girls living below the federal poverty level were significantly less likely to complete vaccination compared to adolescents with household incomes > $75,000 (aOR 0.76; 0.63–0.92) [44].

The effect of SES may differ by delivery strategy; in Canadian public schools with in-school HPV vaccine delivery, completion increased as SES decreased, in Catholic schools in which the pupils relied on community delivery, completion decreased as SES decreased [58]. A linear trend with the Scottish multiple index of deprivation was found with completion but not with initiation; however, the difference between the most and least deprived groups was small (8 %) and disappeared with the administration of a catch-up dose 1 year later [59]. Girls in Canada in 2007–8 living in lower income neighbourhoods were significantly less likely to complete HPV vaccine than girls living in middle income neighbourhoods (aOR 0.45; 0.28–0.72) [33]. In France compliance with the HPV vaccine schedule was lower in social welfare recipients compared to non-recipients (aRR 0.88, 0.83–0.93) [34].

Healthcare utilization

History of health care utilization was inconsistently associated with completion. Seventeen articles from the USA, France and Australia analysed an individual's prior use of health care (defined by receipt of other recommended vaccines, or the number of prior visits to a primary health care provider) and completion of a multi-dose series of varicella, HPV or HBV vaccines. In adjusted analyses in the USA, >10 visits to a health care provider in the last year was associated with 15 % increased likelihood of HPV vaccine completion and a 4–6 % increase in HBV completion [31]. Similar findings were reported in France where compliance with the HPV vaccine regimen was 10 % higher if a girl had >6 consultations with a family physician in the past year [34]. The magnitude of the effect is supported by reports of a 2 % increased likelihood of completing the HPV vaccine series with every primary care provider visit in the past year [36].

A further eight studies found no association between vaccine completion and the number of visits to a primary healthcare in the preceding 2 years [60], non-acute care in the year preceding initiation [29, 33, 39, 44, 55], previous prescriptions [47] or receipt of tetanus, diphtheria, and pertussis booster (Tdap) and meningococcal vaccines [38].

Recorded contraceptive use (DMPA) at any time in the medical records by HPV vaccine recipients was associated with a two-fold increase (95 % CI 1.72–2.47) in the odds of HPV vaccine completion [42]. In Canada, HBV vaccination conferred 16.9 times higher odds (95 % CI 14.8–19.2) for HPV vaccine completion in comparison with those who had not received HBV. However, the association could be confounded by the differing vaccination policies and delivery strategies by school [58]. In Australia in an area with a high risk population, including young sex workers and drug users, a shorter time interval (<2 weeks) between first contact with the health care provider and initiation of vaccine series correlated with better HBV completion [35].

Vaccine related knowledge

Three American studies examined knowledge in relation to completion in multivariate analysis [45, 47, 55]. The ability to correctly identify the number of required doses remained associated with series completion (aRR 1.38; 95 % CI 1.08–1.76) [55]. Parents who remember receiving a provider recommendation for vaccination were more likely to have daughters who had completed the regimen (aOR 2.71; 1.99–3.70) [45]. However, general knowledge of HPV and HBV vaccine was not associated with completion in adjusted analyses [45, 47].

Adverse events

Three studies assessed whether experience of adverse events following HPV vaccination affected series completion in the USA. Parents of daughters who had completed the three dose series reported pain or discomfort as often as parents whose daughters were late for their second or third dose (OR 0.76; 95 % CI 0.33–1.77) [61]. In a survey of over 3000 vaccine recipients [55]

(response rate 27 %), multivariate analysis controlling for age, socio-economic status, health care utilization, showed reports of bruising or swelling at first dose did not affect completion of the series (aRR 0.88; 0.7–1.00). An association was not apparent for those reporting pain, syncope or dizziness [55]. A qualitative study of 18 women in the USA who did not complete the HPV vaccine series found none of them mentioned adverse events as a reason [62].

Risk behaviour

A variety of risk behaviours in seven studies were assessed in relation to completion of HBV or HPV vaccine schedules; no associations were found. Drug use, history of sexually transmitted infections (STIs), or alcohol use was not associated with completion in the USA [38, 47, 63]. In multivariate analysis in Australia, intravenous drug use, sex work, or hepatitis C status did not correlate with likelihood of completion of HPV in a health unit serving at-risk populations [35].

Concomittant healthcare

Three articles assessed the effect of concomitant health service delivery on adherence to HPV in the USA. Receipt of another vaccine at the time of HPV vaccination was not associated with odds of HPV completion controlling for socio-demographic and provider characteristics [55]. However, if the first dose was given at a health care provider visit which was attended primarily for another reason other than HPV, the odds of a mistimed 3rd dose were almost double (aOR 1.97; 95 % CI 1.39–2.80) than that if the first dose was at a vaccine only visit, controlling for age and race [48]. Type of visit was not associated in analysis investigating the effect of age and healthcare utilization [41].

Access

Access to vaccination sites was assessed in two studies in the USA. Compliance to the schedule and completion of the series were not governed by proximity or mode of transportation to the clinical site [47]. Distance from home to clinic was not associated with completion controlling for age, race, and healthcare utilization [40].

Qualitative studies

One qualitative study investigated why 9–26 year olds did not return for the final dose of the HPV vaccine series, in non-exclusive responses: 33 % claimed they didn't know they were meant to obtain further doses, 23 % claimed they were too busy, 15 % cited inconvenience, 38.5 % claimed they were too busy or forgot, 7.7 % claimed they were too busy and times were inconvenient [62]. Two additional surveys of partially vaccinated university students in the USA and Australia indicated the potential problems with vaccinating older age groups who have competing priorities; reasons focused on inconvenience and lack of time [64, 65].

Maternal characteristics

Three studies in the USA analyzed the relationship between maternal preventative behavior (cervical screening) and their daughter's HPV vaccine series completion. In multivariate analysis, controlling for demographic, socio-economic, family, and health plan characteristics, all three studies found that girls whose mothers had received a pap smear in the past three years were more likely to complete the HPV vaccine series (aOR 1.07, 95 % CI 1.06–1.08) [56]; 1.42, 1.31–1.54 [54] and 1.87, 1.31–2.75 [66]).

The relationship between maternal education and vaccine series completion was assessed in eight studies conducted in the USA ($n = 7$) and in Greece [51]. Adolescents whose mothers had less than high school education were less likely to complete the vaccine series in multivariate analysis [44, 66]; both studies controlled for adolescent age, SES, and mother's health characteristics and found similar effect estimates (aOR 0.68; 95 % CI 0.56–0.84) [44]; aOR 0.60; 0.41–0.87 [66]). No association between maternal education and HPV or HAV vaccine series completion in multivariate analysis was found in three studies [39, 45, 50].

Maternal age and marital status were found to have no or very slight associations with vaccine series completion in four of the five included studies [39, 44, 45, 66]. In unadjusted analysis, one study found daughters with mothers aged over 40 years were more likely to complete the HPV vaccine series compared to mothers who were less than 40 years old [56].

Provider/ organisational characteristics

Delivery model

There is strong evidence for high completion rates with school-delivery in high - income and low-middle income countries. Canadian in-school HPV vaccination completion rates were 75 % (95 % CI 74.7–75.8) compared to 36 % (95 % CI 35.3–37.2) for girls provided with a community-delivery model [58]. In-school vaccinations conferred 1.8 times the odds of completing the HBV series compared to if adolescents had to go off-site (95 % CI 1.15–2.8) in a parent survey in the USA controlling for age, race, insurance, SES, prior healthcare utilization [29].

Only 2 articles included data from low and middle - income countries (LMIC); descriptive results are available regarding the success of different delivery strategies [67]. In Uganda, a school-based strategy appeared more successful (94 % completion) than a strategy in which the vaccine was given in the community with a child

health programme (79–87 % completion year 1-year 2) although the delivery strategies had slightly different target populations. Peru's school-based strategy achieved 98.7 % completion, whilst combined school-based and health centre strategies in Vietnam achieved >99 % completion. In India, very similar completion rates were achieved in campaign and routine delivery approaches (97–98 %) [67]. Differences in completion rates achieved in 21 demonstration projects in 14 countries implementing different models of delivery were insignificant [68]; however, the mixed model (school based delivery with mop-up activities at health centres) seemed to confer marginally higher completion (96.6 %), the school-only model was intermediate (88.6 %) and the health facility-only model was least effective (79.7 %)($p = 0.39$) [69].

In Australia, high-risk groups, benefited from an accelerated schedule (0, 7, 21 days and 12 months), which increased the likelihood of HBV vaccine completion 1.35 times (1.01–1.80) controlling for drug use, and length of contact with the health facility [35].

Provider characteristics

Vaccine schedule completion was higher in an American school based programme when students returned the consent forms to their teacher compared to the school nurse [70]. In 1994–5 in Canada, initial parental consent was lower at private schools compared to public schools; however, private and public schools did not differ in completion rates. Different education providers (teachers or public health nurses) did not have an effect on completion, although education from teachers was associated with higher consent [30].

A further 17 studies investigated health provider characteristics, of which 12 reported adjusted analyses. There was no evidence that the speciality of an adolescent girl's primary care physician influenced HPV series completion in multivariate analyses [15, 16, 36, 42, 49, 55]. However, for women >17 years of age in the USA, those with a paediatric/internal medicine physician were slightly less likely to complete the HPV regimen than those with a family medicine physician. Female providers were not significantly associated with completion (male primary care provider aRR0.93 0.85–1.01) [36]. In an American datalink study, those vaccinated at paediatric clinics had the highest completion (61 %) compared to family care practices (53 %; aOR 0.78; 95 % CI 0.76–0.80) and the local health departments (39 %; aOR 0.48; 0.47–0.50) [43].

Discussion

We present a comprehensive review of the available literature on factors influencing adherence to multi-dose vaccine schedules among adolescents. The majority of studies took place in the USA ($n = 49$), the remainder included Canada ($n = 3$), France ($n = 3$), Australia ($n = 2$), Greece ($n = 1$), the UK ($n = 1$) and 2 multi-country studies including LMICs. The two studies including LMICs focused on organisational level factors and reported high adherence to HPV vaccine [68], therefore our summaries of individual level factors are limited in generalizability to developed settings. The high level of variation in the definitions, number and selection of factors investigated in each study limits the comparability of study results and prevented conduct of a meta-analysis. The overall impact of the identified characteristics on vaccine adherence is likely to be dependent on the mix of other factors present, as well as the programmatic and local context.

Good adherence to multi-dose vaccines appears to be higher in early adolescence (9–12 year olds) when compared to later adolescence (>14 years old). It is unclear whether this is linked to adolescent health seeking behaviour, which was inconsistently associated with completion, or whether it is governed by logistical reasons as cited in qualitative results. It could reflect factors which are not explored in the available literature such as which groups were most targeted with communication materials or the general decrease in utilization of health services through adolescence [71]. In some populations in the USA, there is evidence that Black or Hispanic girls are disproportionately prone to low completion rates when compared to White girls after adjustment for socioeconomic status and insurance, despite some reports of similar rates of initiation. Adolescent females may have a slightly elevated likelihood of vaccine completion compared to males; this association may be a symptom of increased opportunity whilst accessing contraception at the health centre. Higher household income, maternal education and maternal preventative health behaviour were associated with higher completion rates when compared to lower socio-economic families and those mothers who rarely sought screening. Insurance status may have a decreasing effect on completion over time as knowledge spreads that both HBV and HPV vaccines are eligible for reimbursement on any insurance plan in the USA. Experience of adverse events and general knowledge about the vaccine did not affect completion rates. School-based delivery alongside supplying vaccine to health centres for out-of-school girls appears to be a successful approach in countries with relatively high school attendance, including some LMICs [69], the UK [59] and Canada [58].

Conclusions

The factors which affect rates of vaccine completion are context and time specific. Providers and programme planners should be aware that obtaining good consent and initiation rates is not enough; sub-groups within the population may need more help than others to complete

the series. Efforts need to continue past the first dose to reduce inequality in completion. Adolescents captured for the first dose remain only partially protected from vaccine related disease until receipt of the final dose of the schedule.

Opportunistic vaccination at the delivery point of other services should be utilized as a strategy to increase vaccine completion. There is no evidence that concomitant service delivery is associated with lower completion. Among 11–18 year olds in Seattle, 71 % of visits to a primary health practitioner in 2006–11 were found to be lost opportunities for dose 3 of HPV vaccine [72]. Especially utilizing visits which were not originally for preventative health care services could rapidly improve completion rates and access those adolescents with low healthcare utilization [71, 72].

A Cochrane review in 2005 found 47 articles detailing the effect of patient reminder/recall on vaccine uptake, all were conducted in developed countries, only one study was conducted in adolescents [73]. In pooled results across all age groups, all reminder/recall systems appeared to improve coverage compared to the control groups. Personal telephone reminders were the most effective intervention (OR 1.92; 95 % CI 1.2–3.07). Letter reminders were close to the effectiveness of phone reminders (OR 1.79; 1.5–2.15), a postcard alone was less effective (OR 1.44; 1.09–1.89), and automated phone calls were least effective (OR 1.29; 1.09–1.53). Interventions to improve completion of vaccine series need to be assessed and the use of novel technologies needs to be explored where electronic records and recall systems are not available.

Additional file

Additional file 1: Table S1. Search terms and results Medline (Ovid SP)1946 to 2014-02-26. (DOCX 17 kb)

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
KEG carried out article screening, synthesis and drafted the manuscript. EK carried out article screening and synthesis. LOE carried out article screening. SM carried out article screening. SM-J carried out article screening (French). MA carried out article screening (Spanish). DAR provided input on the design and methods. DWJ provided input on the design and methods. All authors read, revised and approved the final manuscript.

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4 The association between HPV and subsequent HIV acquisition in Tanzanian and Ugandan women: a nested case-control study (PhD objective 2)

4.1 Preamble

Previous observational studies indicated evidence of a strong association between HPV infection and subsequent HIV acquisition (see Section 1.3)[1-6]. We conducted this nested case-control study using stored cervical samples from previous studies in Tanzania and Uganda to examine the association between HPV infection prevalence, persistence, and clearance and subsequent HIV acquisition. It was proposed that the results would be used to determine the potential effect size of nonavalent HPV vaccination against HIV acquisition.

My supervisor, Deborah Watson-Jones, designed this study with several other colleagues (Kathy Baisley and Richard Hayes). She also secured the funding to conduct the work. I was the study coordinator and one of my initial activities was to input into the selection of samples to test. I coordinated the withdrawal of the selected samples from archive freezers in the Mwanza Intervention Trials Unit (MITU), the reception of samples from Uganda and oversaw the testing of samples in the National Institute for Medical Research (NIMR) laboratory, Mwanza, Tanzania. Samples were tested by laboratory technicians at the NIMR laboratory. I performed internal quality control and cross-checked the interpretation of the results of the Roche Linear Array HPV genotyping assay[7]. I conducted the primary analyses of the results with the advice from my statistical advisor, Kathy Baisley, I wrote the first draft of the manuscript and I led on the responses to reviewers for the paper. I also analysed the results of external quality control testing at the Catalan Institute of Oncology (ICO), Barcelona.

The manuscript is formatted in accordance with the Journal of Infectious Diseases requirements. As this manuscript has already been published, a copy of the 'pdf' as published is included after the text.

Additional information on study methods is included after the manuscript (Section 4.5).

I have presented this work orally at the following forum:

- Symposium on Cervical Cancer in Sub-Saharan Africa; The National Institute for Medical Research – Mbeya Medical Research Centre, Mbeya, Tanzania; 2nd – 3rd November 2015. Oral (40 minutes): **HPV epidemiology and HPV vaccine delivery strategies in low and middle income countries.**

I have presented this work in a poster presentation at the following conference:

- The 30th International Papillomavirus Conference ('HPV 2015'); September 17-21st 2015; Lisbon, Portugal. '**The associations between human papillomavirus prevalence, persistence or clearance and subsequent HIV acquisition in Tanzanian and Ugandan women: a nested case-control study'**. Gallagher K.E., Baisley K., Hayes R., Kapiga S., Vandepitte J., Grosskurth H., Vallely A., Kamali A., De Sanjose S., Changalucha J., Watson-Jones D.

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Principal Supervisor	Deborah Watson-Jones
Thesis Title	Evaluating human papillomavirus vaccine introduction in Tanzania and other low-resource settings

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I selected stored samples from freezers and coordinated testing of samples in the NIMR, Mwanza laboratory. I conducted the statistical analysis and wrote the first draft of the manuscript

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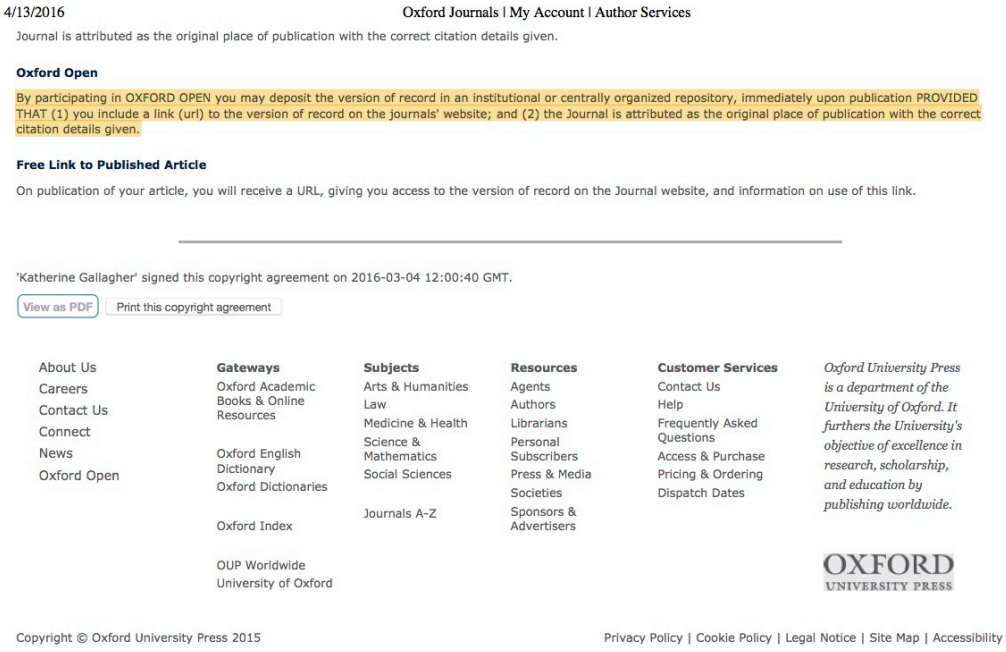

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4.4 Manuscript 2 - The association between cervical human papillomavirus infection and subsequent HIV acquisition in Tanzanian and Ugandan women: a nested case-control study.

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Footnotes

All authors declare no conflicts of interest.

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Abstract presented on the 17th-21st September 2015 at the 30th International Papillomavirus Conference, Lisbon, Portugal (Abstract HPV15-0921).

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Abstract: 198/200 words

Article: 3500/3500 words

Abstract

Objective:

To analyse the associations between cervical human papillomavirus (HPV) infection and HIV acquisition using cervical samples from previous studies in Tanzania and Uganda.

Methods

Women who acquired HIV infection during follow-up (cases n=161) and HIV seronegative controls (individually-matched, n=464) were selected from five cohorts of women working in bars and recreational facilities. Stored cervical samples were tested for 37 HPV genotypes using a PCR assay (Roche Linear Array genotyping assay). Multivariate matched analysis using conditional logistic regression was performed to evaluate HPV infection, persistence and clearance as predictors of HIV acquisition.

Results

HIV seroconverters were significantly more likely than controls to frequently drink alcohol, and to be infected with ***Chlamydia*** *trachomatis, Neisseria gonorrhoeae* or herpes simplex virus type 2 (HSV2). There was no evidence of an association between HIV acquisition and any detectable HPV at the visit prior to HIV seroconversion (aOR1.02, 95%CI 0.66-1.57); nor between HIV acquisition and persistent (Two positive HPV genotype-specific results at least 6-months apart), cleared (a positive HPV result followed by negative HPV genotype-specific result), or newly acquired HPV infection, compared to HPV negative women.

Conclusion

There was no evidence of association between HPV infection status and subsequent HIV acquisition. These results stand in contrast to other observational studies.

Keywords

Human papillomavirus, HIV (transmission, prevention), Sub-Saharan Africa

Introduction

Human papillomavirus (HPV) is a highly prevalent sexually transmitted virus. There are 40 genotypes which infect the genital mucosa[1], 13 of which are regarded as carcinogenic[2]. Persistent infection with carcinogenic 'high-risk' HPV genotypes (HR HPV) is the cause of almost all cases of cervical cancer[3], the third most common cancer among women worldwide[4]. HPV DNA has also been associated with cancerous lesions of the vagina, vulva, penis, anus and the oropharynx[3, 5]. Bivalent (Cervarix®; HPV 16, 18) and quadrivalent (Gardasil®; HPV 6, 11, 16, 18) HPV vaccines are available. A nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) gained FDA approval in December 2014[6]. Over 80% of men and women contract HPV at least once in their lifetime[3, 7]. However, only a small proportion of these infections persist to cause lesions, which can progress to cancer[8, 9]; and 90% of infections are cleared within two years[10].

East African women harbour the highest HPV DNA prevalence in the world (31.7%, 95%CI 29.5-33.8) and experience the highest age-standardised incidence rate of cervical cancer (42.7 /100,000 women/year)[4, 11-13]. In cytologically normal, HIV negative, young women with a median age of 18 years, 73.5% in Tanzania[14] and 73.2% in Uganda[15] were found to have detectable HPV DNA of any genotype. Detection of HPV DNA increases rapidly after HIV seroconversion in HIV-infected women compared with detection rates over time in women who remain HIV-uninfected[16, 17]. HPV is more likely to persist and to progress to cancer in HIV positive and immunosuppressed women[18, 19].

There is growing evidence that HPV may be an important co-factor in HIV acquisition. There is a plausible biological mechanism for this association: weakened cell adhesion caused during HPV infection could expose basal layers of the epithelium in the genital tract and form additional HIV entry points[20, 21]. HPV infection and the mechanisms involved in clearing the infection may cause an influx of inflammatory cytokines[21], macrophages and T-cells[22] creating a favourable environment for HIV invasion. A meta-analysis found an association between detectable HPV DNA and HIV acquisition in seven of eight observational studies in both men and women[23] [24-29]; there was a two-fold increased risk of HIV acquisition in women with prevalent HPV infection with any HPV genotype (HR: 2.06 (95%CI: 1.44–2.94)). Similar associations were observed for infection with HR and LR HPV and in two studies analysing clearance of any genotype[27, 28] but no

association was found with HPV persistence. Since this meta-analysis, two further observational studies in South Africa using cervical samples confirmed the association between any HPV infection and HIV acquisition in women[30, 31]. Two studies in men have shown a positive association between penile HPV clearance and HIV acquisition[32, 33]. Clearance of penile HPV infections was associated with elevated dendritic cell density in the foreskin epidermis[33].

In this paper, we present findings from a nested case-control study undertaken to investigate the association between cervical HPV infection and HIV acquisition using stored cervical samples from five previous studies in the Lake Zone and Kilimanjaro Regions of Tanzania (four studies); and Kampala, Uganda (one study). The extent to which HPV infection, persistence and clearance appear to be predictors for HIV infection is described.

Methods

Study participants & design

Cases (women who acquired HIV infection after enrolment) and controls (women who remained HIV negative) were selected from five previously enrolled cohorts of women aged 16-45 years working in bars, guesthouses, and recreational facilities in urban and semi-urban areas of Tanzania and Uganda (Table 4.1). Recruitment methods for these studies have been described previously [34-37]. All studies recruited women from their place of work, followed them for 12 months or more between 2002 and 2011, and measured the incidence of HIV and other sexually transmitted Infections (STIs) at 3-6 month intervals. There was good retention of participants at 12 months across all studies (range 68%[36]-90%[37]). Participants were interviewed at enrolment and follow-up visits on socio-economic status, education, alcohol and drug usage, sexual behaviour, and family planning practices.

Across the five studies, 178 women were HIV negative at enrolment and seroconverted to HIV during follow-up; of these, 172 attended at least one study visit within 12 months prior to the first detection of HIV and were selected as cases. Cases were individually matched with three randomly selected controls from the same study and who attended the same follow-up visits, but who remained HIV seronegative for the time-points selected and at the first visit after the visits selected for analysis. Controls could become HIV seropositive at a later visit. Of the 688 women from the original sample selection list, 664 women (166 cases and 498

controls; 96.5%) contributed stored samples for testing; five case's samples could not be located in the laboratory archives. If control samples were missing substitute controls were selected. Some HPV test results were invalid; therefore the final sample size comprised 161 cases and 464 controls.

Ethical approval for the four studies in Tanzania had been granted by the Medical Research Coordinating Committee of Tanzania. The Ugandan study had received approval from the Science and Ethics Committee of the Ugandan Virus Research Institute and the Uganda National Committee for Science and Technology. All five studies were approved by the ethics committee of the London School of Hygiene and Tropical Medicine. All participants provided consent for the storage and potential further analysis of their information and samples.

Laboratory methods

None of the studies had previously tested samples for HPV. Cervical samples from study visits pre-HIV seroconversion and when HIV was first detected, or the equivalent visits in controls, were tested for detectable HPV DNA using the Linear Array HPV genotyping assay (Roche, CA)[38]. This test detects 13 high risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and 24 low risk HPV types (6, 11, 26, 40, 42, 53, 54, 55 (also known as 44), 61, 62, 64 (also known as 34), 66, 67, 69, 70, 71, 72, 73, 81, 82, IS39, 83, 84, CP6108 (also known as 89))[4]. As IS39 is regarded as a subtype of HPV 82 these genotype-specific results were combined during analysis into just one variable for HPV 82[1]. Cervical samples were either extracts of buffer in which cervical swabs were washed (four studies), or a supernatant aliquot from a cervical vaginal lavage (CVL; one study), depending on the availability of stored samples. HPV genotyping was carried out in the laboratory of the National Institute for Medical Research (NIMR), Mwanza, according to the manufacturer's instructions. External quality assurance was performed by the Catalan Institute of Oncology (ICO), Barcelona, Spain. A random selection of 102 samples (5%) was tested by both laboratories. There was good agreement in the detection of any HPV (kappa=0.69; Supplementary Table 4.1).

Data on HIV and STIs were obtained from the original study databases. All studies employed more than one test for confirmation of HIV results. The HSV-2 Suppressive Treatment Trial performed parallel ELISAs (Vironosticka Uni-Form II Ag/Ab, bioMerieux BV, and Murex HIV Ag/Ab Combination, Murex Biotech). If results were discordant or indeterminate, HIV-1 p24 antigen enzyme immunoassay (Biorad

Genetic Systems) was used t detect acute infection. A negative or indeterminate result with p24 was confirmed by Western Blot[34]. The Microbicide Feasibility Study employed sequential testing on a gelatin-particle agglutination test (Serodia HIV-1/2, Fujirebio Inc.) followed by confirmatory ELISA (Vironosticka Uni-Form II)[36]. For both the Mwanza Women's Health cohort and the Moshi Vaccines cohort, parallel testing with Rapid Diagnostic tests (RDTs) was performed (SD Bioline HIV-1/2 3.0, Standard Diagnostics Inc., and Determine HIV-1/2, Alere Medical Co. Ltd.); discordant results were confirmed by ELISA (Vironosticka Uniform II plus O and Murex HIV 1.2); discordant EIAs were confirmed by Western Blot (INNO-LIA, Innogenetics NV)[37]. The Uganda Good Health for Women project tested women using a single Determine RDT (Abbott Determine HIV-1/2) with confirmation of positive results using parallel ELISAs (Vironosticka Uni-Form II plus O, Murex HIV 1.2.O). Discordant results were confirmed by Western Blot (Cambridge Calypte)[35].

Syphilis serology was analysed by a rapid plasma reagin test (RPR Biotec) and the *Treponema pallidum* hemagglutination test (TPHA Biotec). Results from both tests were used to define active syphilis (RPR+ TPHA+), past or treated syphilis (RPR- TPHA+), and negative for syphilis (RPR- TPHA- and RPR+ TPHA-) in all but one study. One study only performed TPHA if participants were RPR+. All studies tested serum samples for antibodies to *Herpes simplex* virus type-2 (HSV-2) using a type-specific IgG ELISA (Kalon Biologicals).

Cervical swabs were tested by PCR for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (Amplicor, Roche diagnostic Systems Inc.). Vaginal swabs were used to culture *Trichomonas vaginalis* using In-Pouch (Biomed Diagnostics) and to prepare a Gram stained slide for the detection of bacterial vaginosis using the Nugent score.

Statistical methods

Conditional logistic regression was used to analyse associations between HIV acquisition and the presence of a genotype-specific HPV infection at the visit prior to the HIV seroconversion visit (the s-1 visit), or the equivalent visit in controls; or evidence of any HPV clearance, or persistent HPV infection only, or acquisition only. Clearance was defined as a genotype specific positive result followed by a negative result for the same genotype, regardless of the status of other HPV co-infections. Persistence was defined as detectable infection with the same genotype for six months or more with no evidence of clearance of other genotypes. Acquisition was defined as a negative HPV result followed by a positive HPV result for the same

genotype and no evidence of clearance or persistence of other genotypes. The possible combinations of visits attended by the cases and controls selected for this study and visit classifications are detailed in Figure 4.1. Due to variations in questionnaires, a number of variables identified a priori as potential confounders were recoded to be consistent across studies (Table 4.2).

First, age-adjusted analyses, with age as a categorical variable, were performed on all available covariates identified a priori as potential confounders and common to all study questionnaires in order to assess their association with HIV acquisition (Table 4.2). Information on socio-demographic and behavioural covariates was either from baseline (the enrolment questionnaire) or was time-updated to values at the time of first detection of HIV seroconversion (the index visit; s0). Since STI data were not gathered at every visit, time-updated STI results used data from both the s0 visit and visit before seroconversion (s-1); women were classified as positive for the STI if they had a positive test at either time point.

Next, age-adjusted analyses of the association of HPV with HIV acquisition were performed. Multivariable models to control for potential confounding were then constructed. Variables describing mobility, vaginal cleansing practices, *Trichomonas* infection and presence of genital warts were not included in the multivariable analysis due to missing data. The remaining covariates were assessed iteratively for evidence of a change in the effect estimate for the association of HPV and HIV, starting with covariates with the strongest association with HIV in age-adjusted analyses. To minimise the number of parameters estimated in the model, only covariates that influenced the size of the effect estimate for HPV remained in the multivariate model. Multicollinearity was assessed against a model adjusted only for age. All p-values were generated by likelihood ratio tests. Assuming an HPV prevalence of 30–50% in control subjects, 150 HIV positive cases and 450 HIV negative controls, we calculated we would have ≥80% power to detect an OR of 1.75 or greater for the association between HIV acquisition and HPV infection at the visit before HIV seroconversion.

Results

Across all time points, 90 of the 1258 samples (7%) returned an 'invalid/inhibited' HPV result on first testing. Sixty-six of these samples had sufficient volume to be re-tested; 41 gave a valid HPV result. Valid HPV results were therefore available for 1209 (96%) of samples. At the s-1 time point, 625 out of 664 women (94%; 161

cases, 464 controls) returned valid HPV results and therefore contributed to the main analysis of the association with HPV prevalence.

The mean age of cases and controls at enrolment was 25 years (range 16-45; Table 4.2). A fifth of women were married or living as married (22%). Over 50% of women stated that their main source of income came from restaurant or bar or guesthouse work and 24% identified themselves as local brew or street food sellers. A proportion of those categorised as 'other' may have been sex workers as this was only determined as a separate category in the Ugandan study. Although 49% had completed primary level education, less than18% had some secondary or higher education. In time-updated data from the visit of first detection of HIV (s0) approximately one third of women reported not currently using any form of contraception whilst 57% reported having used a condom at last sex.

Younger age was strongly associated with HIV-seroconversion (p for trend <0.001; Table 4.2). In age-adjusted analysis, women reporting a higher number of lifetime partners, having been paid for sex in the past three months, and those drinking alcohol more frequently had significantly increased odds of HIV seroconversion. Women who had completed primary education had a higher risk than those with incomplete primary education. Women who experienced forced sex during the three months prior to enrolment had a higher risk of HIV seroconversion, but this effect was not statistically significant. At the s0 or the s-1 visit, 10% of cases and controls had *C. trachomatis*, 11% *N. gonorrhoeae*, and 86% of women had evidence of exposure to HSV-2. These infections significantly increased the odds of HIV seroconversion 2.8, 2.6 and 2.0-fold respectively (Table 4.2).

HPV prevalence before HIV acquisition

The median time interval between the s-1 visit and the first visit at which HIV was detected (s0 visit) was three months; 87% of cases and controls had a cervical sample at or less than six months prior to the s0 visit.

At the s-1 visit 49% of women (51.6% of cases, 48.5% of controls) across groups A-D in Figure 4.1 had detectable HPV infection of any genotype. In adjusted analyses, there was no evidence that prevalent infection with any HPV genotype at the visit prior to the first detection of HIV was associated with HIV acquisition (aOR for any HPV 1.02; 95%CI 0.66-1.57; Table 4.3).

Additional analyses of high and low risk types, nonavalent vaccine types (Table 4.3), or restricted to the 87% of participants with s-1 samples collected six months or less before HIV seroconversion (Supplementary Table 4.2) did not show notably different results.

HPV clearance or persistence and HIV acquisition

119 cases and 323 controls had data from at least two time points (groups B-D in Figure 4.1) and were included in the analysis of the association of HPV clearance and/or persistence with HIV acquisition. Among these women, 42% had evidence of clearance of an HPV genotype irrespective of the status of other genotype specific infections (the 'any clearance' group); 10% had evidence of six month persistence with an HPV genotype only (with no evidence of clearance, with/without acquisition of a different genotype); and 13% had evidence of acquisition of an HPV genotype only (with no concurrent clearance or persistence; Table 4.4). Among the 237 women with HPV data from an s-2 visit, 94% had a s-2 cervical sample at, or within, 12 months prior to the s0 visit.

Adjusted analyses based on data from all available time points did not show evidence of an association between the clearance, persistence or acquisition of HPV infection and HIV acquisition (Table 4.4). Additional analyses restricted to s-2 and s-1 time points, and excluding data from the s0 visit when HIV infection could have influenced HPV infection, yielded somewhat larger effect estimates for all associations between HPV and HIV. However, confidence intervals were wide and none of the results were statistically significant (Supplementary Table 4.3).

Discussion

In these cohorts of Tanzanian and Ugandan women there was no evidence of an association between HPV infection, clearance, persistence or acquisition and the odds of HIV acquisition. These results stand in contrast to other observational studies in high-risk women, which found a two-fold increased risk of HIV acquisition in those HPV positive[23]. There is a plausible mechanism by which HPV infection could increase the risk of HIV acquisition through mechanical or immunological changes in the cervix[20-22]. There is strong evidence of cofactor effects of other STIs on HIV transmission[39-46]. We sought to confirm the findings of previous studies and add to limited data on HPV clearance and subsequent HIV acquisition

but we were unable to provide evidence in our study populations for such association.

Strengths of our study include its size; with 161 cases and 464 controls our study is the largest to date. In previous studies the number of HIV seroconverters ranged from 4-145 women[24-26, 28, 47]. The original cohort studies used for our investigation had high retention rates, and the characteristics of cases and controls were very similar. Cases and controls were selected from the same populations and matched to account for different study sites and designs, and individuals' adherence to study procedures. A sensitivity analysis showed that results did not differ between studies using cervical swab specimens and the one study using CVL to diagnose HPV. The risk of misclassification of HIV infection status was low as all studies used confirmatory HIV tests.

There are a number of possible reasons why our results differ from those reported in the literature. Apart from the Ugandan women, who included self-identified sex workers, it could be considered that the remainder of the participants had a lower risk of HIV acquisition than women recruited in previous studies, some of which only recruited sex workers[24, 26]. However, over 80% of both case and controls in our study were HSV2 seropositive. Although cases in previous studies had similarly high HSV2 prevalence, the prevalence in controls was significantly lower in previous studies[27, 47]. Interactions between HPV, other STIs and the cervical-vaginal microbiome are unclear; however, the effect of STIs on HIV acquisition may diminish the relative effect of HPV. External quality control results from the ICO laboratory indicated 'fair' agreement in the detection of HPV genotypes; non-differential misclassification of HPV infection may have diluted the measured effect of HPV on HIV.

Across all exposure variables investigated there was little evidence of confounding. No information on the relative risk status of the participants' sexual partners was available and missing data precluded controlling for *Trichomonas vaginalis* infection, mobility, vaginal cleansing practices, and the presence of genital warts. However, when analysing the available data on these variables there were no significant associations with HIV status. Cases and controls were well balanced with regards to baseline STI infections; however, residual confounding related to differences in sexual behaviour cannot be excluded. The numbers of participants with clearance

and 6-month persistence were small and confidence intervals were wide; the existence of a moderate effect of HPV on HIV acquisition cannot be ruled out.

Our study used samples that had been stored in freezers for three to nine years. Samples that have been paraffin-embedded show good reproducibility[48, 49]; however, the durability of DNA in frozen swab aliquots or CVL after a long-term storage is undocumented. There is some evidence that detection of beta-globin decreases over time leading to a greater number of faint/ invalid results and therefore potential misclassification of HPV infection status. The inclusion of s0 samples in our analysis could limit the temporal relevance of the analysis of clearance and persistence. Acquisition of HIV between the s-1 and s0 time points may have increased the probability of HPV persistence and/or new acquisition of HPV, which was then detectable at the s0 time point[17]. However, these time points have been used in the two previous studies analysing the effect of HPV clearance and persistence on HIV, with similar prevalence of clearance (around 40%)[27, 28]. When restricting our analysis to the s-2 and s-1 time points, the effect estimates were larger; however, confidence intervals were wide and p-values preclude any clear conclusions. All studies of the association between HPV and HIV infection potentially suffer from inadequate methods of defining HPV infection status. More research is needed to find biological markers of newly acquired infection, latent infection, HPV clearance and persistence.

In conclusion, the HIV epidemic remains a serious problem in sub-Saharan Africa, which simultaneously harbours the highest burden of HPV infection in the world[4]. If previous reports are accurate and HPV infection leads to a 2-fold increase in risk of HIV acquisition, the highly effective HPV vaccines could substantially impact rates of HIV acquisition in areas of high HPV incidence. Whilst previous studies suggested that HPV infection enhances the risk of HIV acquisition, our study based on a large data set from five cohorts in East Africa could not confirm this association; more research is needed to clarify these contrasting results. Given the contradictory evidence of an association between HPV and HIV, a cluster randomised controlled trial of phased delivery of HPV vaccine with monitored HIV incidence may be the only way of concluding whether there is a causal relationship between HPV infection and HIV acquisition.

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Figure 4.1 The combinations of original study visits and available HPV results, relative to the visit at which HIV was first detected, attended by cases and controls and selected for analysis

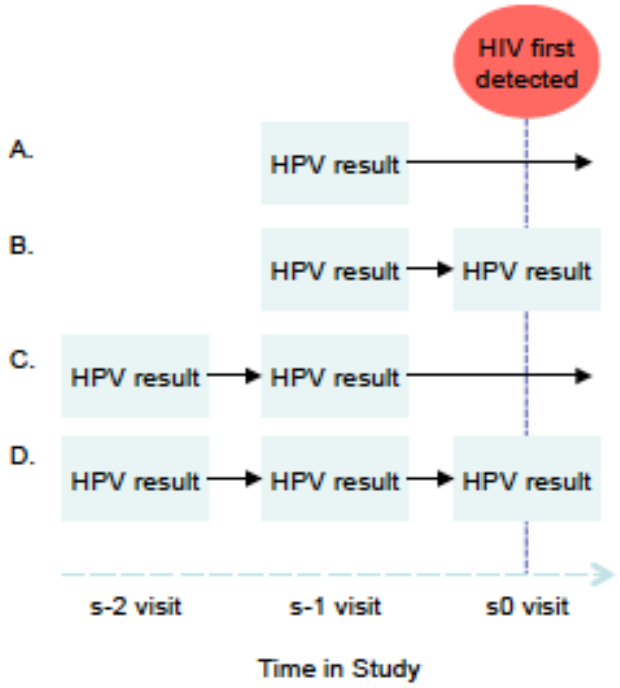

Table 4.1 Summary of five cohort studies from East Africa used for the nested case-control study of the association between HPV infection and HIV acquisition

Study	Study population	Total HIV-negative enrolled	Year	Length of follow up (months)	Relevant Sample type	Frequency of sample collection	Cases N=161	Controls N=464
HSV2 Suppressive Treatment Trial (Lake Zone, Tanzania)	Women working in bars, guesthouses etc. (Age 16-35)	821	2003-2007	30	Blood, Vaginal swab, Cervical swab, CVL	Blood: every 3 months; cervical-vaginal: 0, 6, 12, 24, 30 months	**54**	**154**
Microbicide Feasibility Cohort (Lake Zone, Tanzania)	Women working in bars, guesthouses etc. (Age 16-54)	1156	2002-2004	12	Blood, Vaginal swab, Cervical swab	0, 6, 12 months (3 and 9 month samples taken if symptoms of HIV/ STIs)	**19**	**56**
Women's Health Project (WHP) (Lake Zone, Tanzania)	Women working in bars, guesthouses etc. (Age 18-44)	966	2008-2009	12	Blood, Vaginal swab, Cervical swab, CVL	Blood: 0, 3, 6, 9, 12; Cervical-vaginal: 0, 6, 12 months	**28**	**82**
EDCTP Vaccine Cohort (Kilimanjaro Region, Tanzania)	Women working in bars, guesthouses etc. (Age 18-44)	412	2009-2011	12	Blood, Vaginal swab, Cervical swab	0, 3, 6, 9, 12 months	**14**	**39**
Good Health for Women, (Kampala, Uganda)	Self-reported female sex workers and women working in entertainment (Aged ≥18)	646	2008-2011	18	Blood, Vaginal swab, Cervical swab	0, 3, 6, 9, 12, 18 months (Blood at 15 months also)	**46**	**133**

Table 4.2 Characteristics of the matched cases and controls and age-adjusted associations with case-control status using conditional logistic regression

Characteristics	Cases (%) N=161	Controls (%) N=464	OR age-adjusted (95%CI)	p-value
Enrolment data				
Age Group				
16-24	79 (49.0)	178 (38.4)	1	pT[a]<0.001
25-34	70 (43.5)	208 (44.8)	0.64 (0.41-0.99)	
≥35	12 (7.5)	78 (16.8)	0.28 (0.13-0.57)	
Marital status				
Married/ Living as married	27 (16.8)	109 (23.5)	1	0.221
Separated/ Divorced/ widowed	94 (58.4)	252 (54.3)	1.54 (0.92-2.57)	
Single	40 (24.8)	103 (22.2)	1.22 (0.66-2.25)	
Religion				
Christian	121 (75.2)	326 (70.3)	1	0.495
Muslim	34 (21.1)	121 (26.1)	0.78 (0.49-1.23)	
Other/ No religion	6 (3.7)	17 (3.6)	1.21 (0.46-3.19)	
Main Employment				
Restaurant/bar worker/ cleaner	85 (52.8)	247 (53.2)	1	0.916
Local brew or street food vendor	40 (24.8)	113 (24.4)	1.05 (0.64-1.74)	
Manager/ owner/ office worker	8 (5.0)	34 (7.3)	0.79 (0.33-1.89)	
Sex worker[b]	18 (11.2)	46 (9.9)	1.22 (0.59-2.53)	
None/ Other	10 (6.2)	24 (5.2)	1.26 (0.56-2.80)	
Maximum education level attained				
None/ Incomplete Primary	48 (29.8)	162 (34.9)	1	0.008
Complete Primary	92 (57.1)	214 (46.1)	1.61 (1.04-2.51)	
Some Secondary/ Higher	21 (13.0)	88 (19.0)	0.66 (0.36-1.23)	
Crowding (number of people living in the participant's residence)				
0-2 people	95 (56.9)	248 (50.5)	1	pT[a]= 0.116
3-4 people	45 (27.0)	129 (26.3)	0.64 (0.41-0.99)	
5+	27 (16.2)	114 (23.2)	0.29 (0.14-0.59)	
Lifetime number of sexual partners[c]				
<5	50 (31.9)	179 (39.5)	1	pT[a]= 0.024
5 – 9	39 (24.8)	92 (20.3)	1.71 (1.02-2.87)	
≥10	24 (15.3)	80 (17.7)	1.49 (0.81-2.75)	
Do Not Remember	44 (28.1)	102 (22.5)	2.78 (1.33-5.82)	
Experience of forced sex in the last 3 months before enrolment[d]				
No	121 (77.1)	378 (83.1)	1	0.058
Yes	36 (22.9)	77 (16.9)	1.79 (0.98-3.23)	
Alcohol Consumption			-	
Never	53 (32.9)	193 (41.6)	1	pT[a]=0.003
Monthly – Once a week	9 (5.6)	52 (11.2)	0.60 (0.28-1.32)	
2-3 times a week	47 (29.2)	114 (24.6)	1.75 (1.06-2.91)	
≥4 times per week	52 (32.3)	105 (22.6)	2.02 (1.23-3.33)	
Time-updated data				
Current method of family planning[e]				
Nothing	50 (31.1)	143 (31.4)	1	0.650
Oral Pill	29 (18.0)	84 (18.5)	1.04 (0.58-1.86)	
Injection	45 (28.0)	100 (22.0)	1.30 (0.77-2.17)	
Condom	30 (18.6)	103 (22.6)	0.83 (0.48-1.43)	
Other e.g. traditional/ calendar	7 (4.4)	25 (5.5)	0.93 (0.34-2.57)	
Condom use at last sex[f]				

Characteristics		Cases (%) N=161	Controls (%) N=464	OR age-adjusted (95%CI)	p-value
	No	87 (55.4)	268 (60.1)	1	0.439
	Yes	70 (44.6)	178 (39.9)	1.16 (0.79-1.71)	
Transactional sex in the last 3 months[g]					
	No	85 (53.1)	290 (63.7)	1	0.002
	Yes	75 (46.9)	165 (36.3)	2.18 (0.37-0.98)	
Partners in the last 3 months					
	None/ one	94 (58.8)	298 (65.5)	1	pT[a]=0.148
	2-9	39 (24.4)	89 (19.6)	1.50 (0.91-2.47)	
	≥10	18 (11.3)	54 (11.9)	1.30 (0.58-2.93)	
	Don't remember	9 (5.6)	14 (3.1)	2.52 (0.90-7.00)	
Sexually Transmitted Infections – time updated data using s0 and s-1 results					
Chlamydia trachomatis					
	Negative at all available time points	133 (82.6)	431 (92.9)	1	<0.001
	Positive at one or more time points	28 (17.4)	33 (7.1)	2.76 (1.57-4.87)	
Neisseria gonorrhoeae					
	Negative at all available time points	130 (80.8)	426 (91.8)	1	<0.001
	Positive at one or more time points	31 (19.3)	38 (8.2)	2.58 (1.51-4.41)	
Herpes Simplex-2 virus[h]					
	Negative at all available time points	15 (9.4)	70 (15.2)	1	0.022
	Positive at one or more time points	144 (90.6)	392 (84.9)	2.00 (1.08-3.75)	

[a] P-value for linear trend. In the association with number of partners we assume women who stated "do not remember" had the highest number of partners.

[b]Only the Ugandan study included sex work as a category in answer to the question: 'what is your main source of income?'
[c]Missing data on lifetime number of sexual partners: 15 women (2.4% controls; 2.5% cases)
[d]Missing data on forced sex: 13 women (1.9% controls, 2.5% cases)
[e]Missing data on current use of contraception: 9 women (all were controls).
[f]Missing data on condom use at last sex: 22 women (3.8% controls, 2.5% cases)
[g]Missing data on partners in the last 3 months: 10 women (1 case and 9 controls (2%))
[h]Missing data on HSV-2 infection: 4 women (2 cases and 2 controls)

Table 4.3 Associations between HPV infection at the visit preceding the first detection of HIV seroconversion (the s-1 visit) and subsequent HIV acquisition among women with a valid HPV result at the s-1 visit

HPV infection status at the study visit preceding HIV seroconversion (s-1)	Cases (%) N=161	Controls (%) N=464	Age-adjusted OR (95%CI) (p-value)	aOR1[a] (N=160/455) (p-value)	aOR2[b] (N=158/454) (p-value)
Any HPV			0.783	0.923	0.926
HPV uninfected	78 (48.5)	239 (51.5)	1	1	1
Any HPV infection	83 (51.6)	225 (48.5)	1.06 (0.72-1.56)	1.02 (0.68-1.53)	1.02 (0.66-1.57)
Nonavalent vaccine types			0.867	0.875	0.901
HPV uninfected	78 (48.5)	239 (51.5)	1	1	1
Nonavalent HPV infection	38 (23.6)	103 (22.2)	0.99 (0.61-1.60)	0.95 (0.57-1.56)	0.95 (0.56-1.61)
Other HPV+ infection	45 (28.0)	122 (26.3)	1.12 (0.71-1.75)	1.09 (0.68-1.75)	1.08 (0.66-1.78)
HR/LR HPV infection			0.667	0.738	0.658
HPV uninfected	78 (48.5)	239 (51.5)	1	1	1
HR HPV infection only	27 (16.8)	70 (15.1)	1.08 (0.63-1.85)	1.07 (0.60-1.89)	1.15 (0.63-2.08)
LR HPV infection only	33 (20.5)	83 (17.9)	1.26 (0.75-2.12)	1.19 (0.69-2.06)	1.17 (0.66-2.08)
HR-LR HPV co-infection	23 (14.3)	72 (15.5)	0.85 (0.48-1.48)	0.82 (0.45-1.47)	0.78 (0.43-1.44)

[a] aOR1 adjusted for variables which influenced the effect estimate of the association between any HPV at s1 and HIV i.e. age group, alcohol consumption at enrolment, and transactional sex in the 3 months prior to first detection of HIV (time updated variable).
[b] aOR2 adjusted for the same variables as for aOR1 and additionally the time-updated STI variables CT, NG, HSV-2. Women were classified as positive for CT, NG, or HSV2 if they had results for at least one of the s0 or the s-1 visits and at least one result was positive.

Table 4.4 Associations of HPV persistence, clearance and acquisition with subsequent HIV infection among women who had valid HPV results for at least 2 time points

HPV persistence, clearance, acquisition prior to HIV seroconversion[a]	Cases (%)	Controls (%)	Age-adjusted OR (95%CI) (p-value)	aOR1[b] (95%CI) (p-value)	aOR2[c] (95%CI) (p-value)
Amongst all women with >1 valid result (s0, s-1, or s-2)	N=119	N=323	0.771	(N=118/319) 0.765	(N=117/319) 0.685
Uninfected	37 (31.1)	118 (36.5)	1	1	1
Any HPV clearance	53 (44.5)	134 (41.5)	1.17 (0.68-2.00)	1.08 (0.61-1.89)	0.85 (0.46-1.55)
HPV 6m persistence +/- acquisition	10 (8.4)	33 (10.2)	0.97 (0.41-2.28)	0.94 (0.39-2.27)	0.93 (0.37-2.29)
HPV Acquisition only	19 (16.0)	38 (11.8)	1.42 (0.68-2.95)	1.44 (0.68-3.04)	1.33 (0.61-2.90)

[a] HPV classifications: 'Uninfected' consists of women who remained HPV negative at all available time points; 'Any HPV clearance' includes women who had evidence of any HPV clearance, a genotype specific HPV positive result followed by a genotype specific HPV negative result, regardless of concurrent HPV persistence or acquisition; 'HPV 6m persistence' category included women with at least 2 genotype specific positive results at least 6 months apart with or without evidence of acquisition of other genotypes; 'Acquisition only' included women who only had evidence of a genotype specific negative HPV result followed by a positive result for the same genotype at a later time point with no evidence of persistence or clearance of other genotypes.

[b] aOR1 is adjusted for age group, alcohol consumption at enrolment as a linear variable and transactional sex in the 3 months prior to first detection of HIV (i.e. the same model as used for the analysis of the effect of prevalent HPV in Table 4.3; all other covariates were checked but no other residual confounding was found).

[c] aOR2 is adjusted for age, alcohol consumption at enrolment as a linear variable, transactional sex, CT and HSV2 detected at first detection of HIV or the previous visit. NG was removed from the model to reduce the number of parameters as it did not affect the aOR.

Supplementary Table 4.1: External quality assurance results; 102 samples tested at the National Institute for Medical Research (NIMR), Mwanza were re-tested by the Catalan Institute of Oncology (ICO), Barcelona[a]

HPV genotypes	ICO		
NIMR	**-**	**+**	**Total**
-	2869	51	2920
+	41	108	149
Total	2910	159	3069

[a] 102 samples were randomly selected for re-testing at the ICO laboratory using Roche Linear Array for 37 different genotypes; 9 samples gave inhibited results on retesting at ICO; 4 genotypes were excluded from comparison due to differences in reporting practices at the 2 institutions (HPV 52, 33, 35, 58). This gave 3069 pairs of results for quality assurance (93 samples x 33 genotypes). Overall percentage agreement: 97%; Positive percentage agreement: 68%; Negative percentage agreement: 99%; Kappa statistic for agreement between the laboratories: 0.69.

Supplementary Table 4.2: Results when restricted to s-1 samples collected within 6 months of ft detection of HIV.

HPV infection status at the study visit preceding HIV seroconversion (s-1) among samples within 6 months	Cases (%) N=140	Controls (%) N=405	Age-adjusted OR (95%CI) (p-value)	aOR1[a] (95%CI) (N=140/398) (p-value)	aOR2[b] (95%CI) (N=138/397) (p-value)
Any HPV			0.540	0.590	0.599
HPV uninfected	67 (47.9)	211 (52.1)	1	1	1
Any HPV infection	73 (52.1)	194 (47.9)	1.14 (0.75-1.73)	1.13 (0.73-1.75)	1.13 (0.71-1.82)
Nonavalent vaccine types			0.680	0.612	0.625
HPV uninfected	67 (47.9)	211 (52.1)	1	1	1
Nonavalent HPV infection	35 (25.0)	94 (23.2)	1.04 (0.63-1.73)	1.00 (0.59-1.69)	1.00 (0.57-1.75)
Other HPV+ infection	38 (27.1)	100 (24.7)	1.24 (0.76-2.04)	1.27 (0.76-2.14)	1.28 (0.74-2.22)
HR/LR HPV infection			0.669	0.738	0.658
HPV uninfected	67 (47.9)	211 (52.1)	1	1	1
HR HPV infection only	23 (16.4)	61 (15.1)	1.09 (0.61-1.96)	1.11 (0.60-2.03)	1.20 (0.63-2.27)
LR HPV infection only	30 (21.4)	71 (17.5)	1.42 (0.81-2.49)	1.45 (0.80-2.62)	1.46 (0.78-2.73)
HR-LR HPV co-infection	20 (14.3)	62 (15.3)	0.94 (0.51-1.70)	0.89 (0.47-1.66)	0.83 (0.43-1.60)

[a] aOR1 is adjusted for variables which influenced the effect estimate of the association between any HPV at s1 and HIV i.e. age group, alcohol consumption at enrolment, and transactional sex in the 3 months prior to first detection of HIV (time updated variable).
[b] aOR2 is adjusted for those variables in aOR1 and additionally the time-updated STI variables CT, NG, HSV-2. Women were classified as positive for CT, NG, or HSV2 if they had results for at least one of the s0 or the s-1 visits and at least one result was positive.

Supplementary Table 4.3: Associations of HPV persistence, clearance and acquisition with subsequent HIV infection among women who had valid HPV results for at least 2 time points, restricted to selected time points.

HPV persistence, clearance, acquisition prior to HIV seroconversion[a]	Cases (%)	Controls (%)	Age-adjusted OR (95%CI) (p-value)	aOR1[b] (95%CI) (p-value)	aOR2[c] (95%CI) (p-value)
Among s-1 and s0 samples only	N=78	N=209	0.664	N=77/209 0.482	N=77/209 0.226
Uninfected	32 (41.0)	84 (40.2)	1	1	1
Any HPV clearance	26 (33.3)	79 (37.8)	0.79 (0.42-1.49)	0.70 (0.36-1.36)	0.54 (0.26-1.10)
HPV 6m persistence only	4 (5.1)	15 (7.2)	0.60 (0.17-2.08)	0.52 (0.14-1.95)	0.46 (0.12-1.74)
HPV Acquisition only	16 (20.5)	31 (14.8)	1.17 (0.53-2.60)	1.16 (0.51-2.63)	1.08 (0.45-2.56)
Among s-2 and s-1 samples only	N=62	N=169	0.547	N=62/165 0.612	N=61/165 0.828
Uninfected	17 (27.4)	67 (39.6)	1	1	1
Any HPV clearance	31 (50.0)	67 (39.6)	1.83 (0.80-4.23)	1.70 (0.71-4.10)	1.08 (0.41-2.85)
HPV 6m persistence only	5 (8.1)	14 (8.3)	1.68 (0.46-6.20)	2.09 (0.54-8.04)	1.93 (0.46-8.02)
HPV Acquisition only	9 (14.5)	21 (12.4)	1.51 (0.52-4.35)	1.66 (0.56-4.97)	1.17 (0.35-3.87)

[a] HPV classifications: 'Uninfected' consists of women who remained HPV negative at all available time points; 'Any HPV clearance' includes women who had evidence of any HPV clearance, a genotype specific HPV positive result followed by a genotype specific HPV negative result, regardless of concurrent HPV persistence or acquisition; 'HPV 6m persistence' category included women with at least 2 genotype specific positive results at least 6 months apart with or without evidence of acquisition of other genotypes; 'Acquisition only' included women who only had evidence of a genotype specific negative HPV result followed by a positive result for the same genotype at a later time point with no evidence of persistence or clearance of other genotypes.

[b] aOR1 adjusted for age group, alcohol consumption at enrolment as a linear variable and transactional sex in the 3 months prior to first detection of HIV (i.e. the same model as used for the analysis of the effect of prevalent HPV in Table 4.3; all other covariates were checked but no other residual confounding was found).

[c] aOR2 is adjusted for age, alcohol consumption at enrolment as a linear variable, transactional sex, CT and HSV2 detected at first detection of HIV or the previous visit. NG was removed from the model to reduce the number of parameters as it did not affect the aOR.

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MAJOR ARTICLE

The Association Between Cervical Human Papillomavirus Infection and Subsequent HIV Acquisition in Tanzanian and Ugandan Women: A Nested Case-Control Study

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Objective. This study was performed to analyze the associations between cervical human papillomavirus (HPV) infection and human immunodeficiency virus (HIV) acquisition, using cervical samples from previous studies in Tanzania and Uganda.

Methods. A total of 161 adult women who acquired HIV infection during follow-up and 464 individually matched HIV-seronegative controls were selected from 5 cohorts of women working in bars and recreational facilities. Stored cervical samples were tested for 37 HPV genotypes, using a polymerase chain reaction assay (Roche Linear Array genotyping assay). Multivariate matched analysis using conditional logistic regression was performed to evaluate HPV infection, persistence, and clearance as predictors of HIV acquisition.

Results. HIV seroconverters were significantly more likely than controls to frequently drink alcohol and to be infected with *Chlamydia trachomatis, Neisseria gonorrhoeae*, or herpes simplex virus type 2. There was no evidence of an association between HIV acquisition and any detectable HPV at the visit prior to HIV seroconversion (adjusted odds ratio, 1.02; 95% confidence interval, .66–1.57) or between HIV acquisition and persistent HPV infection (defined as 2 positive HPV genotype–specific test results at least 6 months apart), cleared HPV infection (defined as a positive HPV test result followed by negative HPV genotype–specific test result), or newly acquired HPV infection, compared with HPV-negative women.

Conclusions. There was no evidence of association between HPV infection status and subsequent HIV acquisition. These results stand in contrast to other observational studies.

Keywords. human papillomavirus; HIV (transmission, prevention); Sub-Saharan Africa.

Human papillomavirus (HPV) is a highly prevalent sexually transmitted virus. There are 40 genotypes that infect the genital mucosa [1], 13 of which are regarded as carcinogenic [2]. Persistent infection with carcinogenic HPV (ie, high-risk HPV [HR-HPV]) genotypes is the cause of almost all cases of cervical cancer [3], the third most common cancer among women worldwide [4]. HPV DNA has also been associated with cancerous lesions of the vagina, vulva, penis, anus, and oropharynx [3, 5]. Bivalent (Cervarix; covering HPV 16 and 18) and quadrivalent (Gardasil; covering HPV 6, 11, 16, and 18) HPV vaccines are available. A nonavalent vaccine (covering HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) gained Food and Drug Administration approval in December 2014 [6]. More than 80% of men and women contract HPV at least once in their lifetime [3, 7]. However, only a small proportion of these infections persist to cause lesions, which can progress to cancer [8, 9], and 90% of infections are cleared within 2 years [10].

East African women harbor the highest HPV DNA prevalence in the world (31.7%; 95% confidence interval [CI], 29.5–33.8) and experience the highest age-standardized incidence rate of cervical cancer (42.7 cases/100 000 women/year) [4, 11–13]. Among cytologically normal, human immunodeficiency virus (HIV)–negative, young women with a median age of 18 years, 73.5% in Tanzania [14] and 73.2% in Uganda [15] were found to have detectable HPV DNA of any genotype. Detection of HPV DNA increases rapidly after HIV seroconversion in HIV-infected women, compared with detection rates over time in women who remain HIV uninfected [16, 17]. HPV is more likely to persist and to progress to cancer in HIV-positive and immunosuppressed women [18, 19].

There is growing evidence that HPV may be an important cofactor in HIV acquisition. There is a plausible biological mechanism for this association: weakened cell adhesion caused by

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HPV infection could expose basal layers of the epithelium in the genital tract and form additional HIV entry points [20, 21]. HPV infection and the mechanisms involved in its clearance may cause an influx of inflammatory cytokines [21], macrophages, and T cells [22], creating a favorable environment for HIV invasion. A meta-analysis found an association between detectable HPV DNA and HIV acquisition in 7 of 8 observational studies of both men and women [23, 24–29]; there was a 2-fold increased risk of HIV acquisition among women with prevalent HPV infection with any HPV genotype (hazard ratio, 2.06; 95% CI, 1.44–2.94). Similar associations were observed for infection with HR HPV and low-risk HPV (LR-HPV) genotypes and in 2 studies analyzing the clearance of any genotype [27, 28], but no association was found with HPV persistence. Since this meta-analysis, 2 further observational studies in South Africa that investigated cervical samples confirmed the association between any HPV infection and HIV acquisition in women [30, 31]. Two studies involving men have shown a positive association between penile HPV clearance and HIV acquisition [32, 33]. Clearance of penile HPV infections was associated with elevated dendritic cell density in the foreskin epidermis [33].

In this article, we present findings from a nested case-control study undertaken to investigate the association between cervical HPV infection and HIV acquisition, using stored cervical samples from 5 previous studies in the Lake Zone and Kilimanjaro regions of Tanzania (4 studies) and Kampala, Uganda (1 study). The extent to which HPV infection, persistence, and clearance appear to be predictors for HIV infection is described.

METHODS

Study Participants and Design

Cases (women who acquired HIV infection after enrollment) and controls (women who remained HIV negative) were selected from 5 previously enrolled cohorts of women aged 16–45 years working in bars, guesthouses, and recreational facilities in urban and semiurban areas of Tanzania and Uganda (Table 1). Recruitment methods for these studies have been described previously [34–37]. All studies recruited women from their place of work, followed them for ≥12 months between 2002 and 2011, and measured the incidence of HIV infection and other sexually transmitted infections (STIs) at 3–6-month intervals. There was good retention of participants at 12 months across all studies (range, 68% [36] to 90% [37]). Participants were interviewed at enrollment and follow-up visits on socioeconomic status, education level, alcohol and drug usage, sexual behavior, and family-planning practices.

Across the 5 studies, 178 women were HIV negative at enrollment and seroconverted to HIV during follow-up; of these, 172 attended at least 1 study visit ≤12 months before the first detection of HIV and were selected as cases. Cases were individually matched with 3 randomly selected controls from the same study who attended the same follow-up visits but remained HIV seronegative at the time points selected and at the first visit after the visits selected for analysis. Controls could become HIV seropositive at a later visit. Of the 688 women from the original sample selection list, 664 (166 cases and 498 controls [96.5%]) contributed stored samples for testing; samples from 6 cases could not be located in the laboratory archives. If control samples were missing, substitute controls were selected. Some HPV test

Table 1. Summary of 5 Cohort Studies From East Africa That Were Used for the Nested Case-Control Study of the Association Between Human Papillomavirus Infection and Human Immunodeficiency Virus (HIV) Acquisition

Study (Location)	Population	HIV-Negative Enrollees, No.	Period	Follow-up Duration, mo	Relevant Sample Types	Sample Collection Frequency	Cases (n = 161)	Controls (n = 464)
HSV2 Suppressive Treatment Trial (Lake Zone, Tanzania)	Women working in settings such as bars and guesthouses; age 16–35 y	821	2003–2007	30	Blood, vaginal swab, cervical swab, CVL	Blood: every 3 mo; cervical-vaginal: 0, 6, 12, 24, 30 mo	54	154
Microbicide Feasibility Cohort (Lake Zone)	Women working in settings such as bars and guesthouses; age 16–54 y	1156	2002–2004	12	Blood, vaginal swab, cervical swab	0, 6, 12 mo (and at 3 and 9 mo for those with symptoms of HIV infection/STIs)	19	56
Women's Health Project (Lake Zone)	Women working in settings such as bars and guesthouses; age 18–44 y	966	2008–2009	12	Blood, vaginal swab, cervical swab, CVL	Blood: 0, 3, 6, 9, 12; cervical-vaginal: 0, 6, 12 mo	28	82
EDCTP Vaccine Cohort (Kilimanjaro Region, Tanzania)	Women working in settings such as bars and guesthouses; age 18–44 y	412	2009–2011	12	Blood, vaginal swab, cervical swab	0, 3, 6, 9, 12 mo	14	39
Good Health for Women, (Kampala, Uganda)	Self-reported female sex workers and women working in entertainment; age ≥18 y	646	2008–2011	18	Blood, vaginal swab, cervical swab	0, 3, 6, 9, 12, 18 mo (blood was also collected at 15 mo)	46	133

Abbreviations: CVL, cervico-vaginal lavage; STI, sexually transmitted infection.

results were invalid; therefore, the final sample size comprised 161 cases and 464 controls.

Ethics approval for the 4 studies in Tanzania had been granted by the Medical Research Coordinating Committee of Tanzania. The Ugandan study had received approval from the Science and Ethics Committee of the Ugandan Virus Research Institute and the Uganda National Committee for Science and Technology. All 5 studies were approved by the ethics committee of the London School of Hygiene and Tropical Medicine. All participants provided consent for the storage and potential further analysis of their information and samples.

Laboratory Methods

None of the studies had previously tested samples for HPV. Cervical samples from study visits before HIV seroconversion and when HIV was first detected, as well as those from the equivalent visits in controls, were tested for detectable HPV DNA, using the Linear Array HPV genotyping assay (Roche, Pleasanton, California) [38]. This test detects 13 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 24 LR-HPV types (6, 11, 26, 40, 42, 53, 54, 55 [also known as 44], 61, 62, 64 [also known as 34], 66, 67, 69, 70, 71, 72, 73, 81, 82, IS39, 83, 84, and CP6108 [also known as 89]) [4]. As IS39 is regarded as a subtype of HPV 82, these genotype-specific results were combined during analysis into just 1 variable for HPV 82 [1]. Cervical samples were either extracts of buffer in which cervical swabs were washed (4 studies) or a supernatant aliquot from a cervico-vaginal lavage (CVL) specimen (1 study), depending on the availability of stored samples. HPV genotyping was performed in the laboratory of the National Institute for Medical Research (NIMR), Mwanza, according to the manufacturer's instructions. External quality assurance was performed by the Catalan Institute of Oncology (ICO), Barcelona, Spain. A random selection of 102 samples (5%) was tested by both laboratories. There was good agreement in the detection of any HPV ($\kappa = 0.69$; Supplementary Table 1).

Data on HIV infection and STIs were obtained from the original study databases. All studies used >1 test for confirmation of HIV results. The HSV-2 Suppressive Treatment Trial performed parallel enzyme-linked immunosorbent assays (ELISAs; Vironosticka Uni-Form II Ag/Ab [bioMerieux, Marcy l'Etoile, France] and Murex HIV Ag/Ab Combination [Murex Biotech, Dartford, UK]). If results were discordant or indeterminate, HIV-1 p24 antigen enzyme immunoassay (EIA; Biorad Genetic Systems, Hemel Hempstead, UK) was used to detect acute infection. A negative or indeterminate result with the p24 antigen EIA was confirmed by Western blot [34]. The Microbicide Feasibility Study used sequential testing on a gelatin-particle agglutination test (Serodia HIV-1/2; Fujirebio, Tokyo, Japan), followed by a confirmatory ELISA (Vironosticka Uni-Form II) [36]. For both the Mwanza Women's Health cohort and the Moshi Vaccines cohort, parallel testing with rapid diagnostic tests (RDTs) was performed (SD Bioline HIV-1/2 3.0 [Standard Diagnostics, Gyeonggi-do, Republic of Korea] and Determine HIV-1/2 [Alere Medical, Waltham, Massachusetts]); discordant results were confirmed by ELISA (Vironosticka Uniform II plus O and Murex HIV 1.2); discordant EIA results were confirmed by Western blot (INNO-LIA; Innogenetics, Ghent, Belgium) [37]. The Uganda Good Health for Women project tested women using a single Determine rapid diagnostic test (Abbott Determine HIV-1/2) with confirmation of positive results using parallel ELISAs (Vironosticka Uni-Form II plus O, Murex HIV 1.2.O). Discordant results were confirmed by Western blot (Cambridge Calypte, Portland, Oregon) [35].

Serological tests for syphilis were analyzed by a rapid plasma regain (RPR) test (Biotec, Birdport, UK) and the *Treponema pallidum* hemagglutination (TPHA) test (Biotec). Results from both tests were used to define active syphilis (positive results of both tests), past or treated syphilis (a negative result of the RPR test and a positive result of the TPHA test), and negative for syphilis (negative results of both tests or a positive result of the RPR test and a negative result of the TPHA test) in all but 1 study. One study only performed the TPHA test if participants had a positive result of the RPR test. All studies tested serum samples for antibodies to herpes simplex virus type 2 (HSV-2), using a type-specific immunoglobulin ELISA (Kalon Biologicals, Guildford, UK).

Cervical swabs were tested by polymerase chain reaction analysis for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (Amplicor; Roche). Vaginal swabs were used to culture *Trichomonas vaginalis*, using In-Pouch (Biomed Diagnostics, White City, Oregon), and to prepare a Gram-stained slide for the detection of bacterial vaginosis, using the Nugent score.

Statistical Methods

Conditional logistic regression was used to analyze associations between HIV acquisition and (1) the presence of an HPV genotype–specific infection at the visit prior to the HIV seroconversion visit (the $s-1$ visit), or at the equivalent visit in controls, (2) evidence of any HPV clearance, persistent HPV infection only, or HPV acquisition only. Clearance was defined as a genotype-specific positive test result followed by a negative test result for the same genotype, regardless of the status of other HPV coinfections. Persistence was defined as detectable infection with the same genotype for ≥6 months with no evidence of clearance of other genotypes. Acquisition was defined as a negative HPV test result followed by a positive HPV test result for the same genotype and no evidence of clearance or persistence of other genotypes. The possible combinations of visits attended by the cases and controls selected for this study and visit classifications are detailed in Figure 1. Owing to variations in questionnaires, a number of variables identified a priori as potential confounders were recoded to be consistent across studies (Table 2).

First, age-adjusted analyses, with age as a categorical variable, were performed on all available covariates identified a priori as

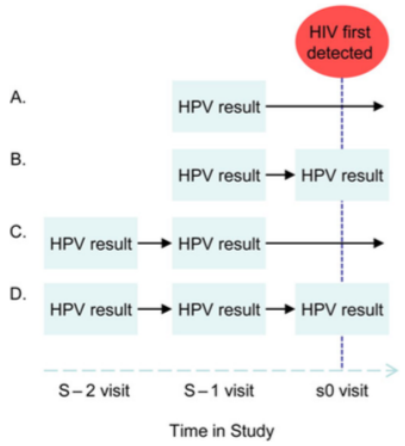

Figure 1. Combinations of original study visits and available human papillomavirus (HPV) test results, relative to the visit at which human immunodeficiency virus (HIV) was first detected, attended by cases and controls and selected for analysis. The s – 1 visit denotes the visit preceding the visit during which HIV seroconversion was detected, and the s – 2 visit denotes the visit preceding the s – 1 visit.

potential confounders and common to all study questionnaires, to assess their association with HIV acquisition (Table 2). Information on sociodemographic and behavioral covariates was either from baseline (the enrollment questionnaire) or time-updated to values at the time of first detection of HIV seroconversion (the index visit; s0). Since STI data were not gathered at every visit, time-updated STI results used data from both the s0 visit and the s – 1 visit; women were classified as positive for the STI if they had a positive test result at either time point.

Next, age-adjusted analyses of the association of HPV with HIV acquisition were performed. Multivariable models to control for potential confounding were then constructed. Variables describing mobility, vaginal cleansing practices, *Trichomonas* infection, and presence of genital warts were not included in the multivariable analysis because of missing data. The remaining covariates were assessed iteratively for evidence of a change in the effect estimate for the association of HPV and HIV, starting with covariates with the strongest association with HIV in age-adjusted analyses. To minimize the number of parameters estimated in the model, only covariates that influenced the size of the effect estimate for HPV remained in the multivariate model. Multicollinearity was assessed against a model adjusted only for age. All *P* values were generated by likelihood ratio tests. Assuming an HPV prevalence of 30%–50% in control subjects, 150 HIV-positive cases and 450 HIV-negative controls, we calculated that we would have ≥80% power to detect an odds ratio (OR) of ≥1.75 for the association between HIV acquisition and HPV infection at the visit before HIV seroconversion.

RESULTS

Across all time points, 90 of the 1258 samples (7%) returned an invalid/inhibited HPV result on first testing. Sixty-six of these samples had sufficient volume to be retested; 41 gave a valid HPV result. Valid HPV results were therefore available for 1209 samples (96%). At the s – 1 time point, 625 of 664 women (94%; 161 cases and 464 controls) returned valid HPV test results and therefore contributed to the main analysis of the association between HIV status and HPV prevalence.

The mean age of cases and controls at enrollment was 25 years (range 16–45 years; Table 2). One fifth of women (22%) were married or living as married. Over 50% of women stated that their main source of income came from restaurant or bar or guesthouse work and 24% identified themselves as local brew or street food sellers. A proportion of those whose income source was categorized as "other" may have been sex workers, as this was only determined as a separate category in the Ugandan study. Although 49% had completed primary education, <18% had some secondary or higher education. In time-updated data from the visit of first detection of HIV (s0) approximately one third of women reported not currently using any form of contraception, whereas 57% reported having used a condom at last sex.

Younger age was strongly associated with HIV seroconversion ($P_{trend} < .001$; Table 2). In age-adjusted analysis, women reporting a higher number of lifetime partners, having been paid for sex in the past 3 months, and those drinking alcohol more frequently, had a significantly increased odds of HIV seroconversion. Women who had completed primary education had a higher risk than those with incomplete primary education. Women who experienced forced sex during the 3 months prior to enrollment had a higher risk of HIV seroconversion, but this effect was not statistically significant. At the s0 or the s – 1 visit, 10% of cases and controls had *C. trachomatis* infection, 11% had *N. gonorrhoeae* infection, and 86% had evidence of exposure to HSV-2. These infections significantly increased the odds of HIV seroconversion by 2.8-, 2.6-, and 2.0-fold, respectively (Table 2).

HPV Prevalence Before HIV Acquisition

The median interval between the s – 1 visit and the first visit at which HIV was detected (the s0 visit) was 3 months; 87% of cases and controls had a cervical sample at or <6 months prior to the s0 visit.

At the s – 1 visit, 49% of women (51.6% of cases and 48.5% of controls) across groups A–D in Figure 1 had detectable HPV infection of any genotype. In adjusted analyses, there was no evidence that prevalent infection with any HPV genotype at the visit prior to the first detection of HIV was associated with HIV acquisition (adjusted OR for any HPV type infection, 1.02; 95% CI, .66–1.57; Table 3).

Table 2. Characteristics of the Matched Cases and Controls and Age-Adjusted Associations With Case-Control Status, Using Conditional Logistic Regression

Characteristic	Cases, No. (%) (n = 161)	Controls, No. (%) (n = 464)	Age-Adjusted OR (95% CI)	*P* Value
Enrollment data				
Age group, y				
16–24	79 (49.0)	178 (38.4)	1	<.001[a]
25–34	70 (43.5)	208 (44.8)	0.64 (.41–.99)	
≥35	12 (7.5)	78 (16.8)	0.28 (.13–.57)	
Marital status				
Married/living as married	27 (16.8)	109 (23.5)	1	.221
Separated/divorced/widowed	94 (58.4)	252 (54.3)	1.54 (.92–2.57)	
Single	40 (24.8)	103 (22.2)	1.22 (.66–2.25)	
Religion				
Christian	121 (75.2)	326 (70.3)	1	.495
Muslim	34 (21.1)	121 (26.1)	0.78 (.49–1.23)	
Other/no religion	6 (3.7)	17 (3.6)	1.21 (.46–3.19)	
Main occupation				
Restaurant/bar worker/cleaner	85 (52.8)	247 (53.2)	1	.916
Local brew or street food vendor	40 (24.8)	113 (24.4)	1.05 (.64–1.74)	
Manager/owner/office worker	8 (5.0)	34 (7.3)	0.79 (.33–1.89)	
Sex worker[b]	18 (11.2)	46 (9.9)	1.22 (.59–2.53)	
None/other	10 (6.2)	24 (5.2)	1.26 (.56–2.80)	
Maximum education level				
None/incomplete primary	48 (29.8)	162 (34.9)	1	.008
Complete primary	92 (57.1)	214 (46.1)	1.61 (1.04–2.51)	
Some secondary/higher	21 (13.0)	88 (19.0)	0.66 (.36–1.23)	
Crowding[c]				
0–2	95 (56.9)	248 (50.5)	1	.116[a]
3–4	45 (27.0)	129 (26.3)	0.64 (.41–.99)	
≥5	27 (16.2)	114 (23.2)	0.29 (.14–.59)	
Lifetime no. of sex partners[d]				
<5	50 (31.9)	179 (39.5)	1	.024[a]
5–9	39 (24.8)	92 (20.3)	1.71 (1.02–2.87)	
≥10	24 (15.3)	80 (17.7)	1.49 (.81–2.75)	
Do not remember	44 (28.1)	102 (22.5)	2.78 (1.33–5.82)	
Forced sex[e]				
No	121 (77.1)	378 (83.1)	1	.058
Yes	36 (22.9)	77 (16.9)	1.79 (.98–3.23)	
Alcohol consumption				
Never	53 (32.9)	193 (41.6)	1	.003[a]
1 time/wk or less	9 (5.6)	52 (11.2)	0.60 (.28–1.32)	
2–3 times/wk	47 (29.2)	114 (24.6)	1.75 (1.06–2.91)	
≥4 times/wk	52 (32.3)	105 (22.6)	2.02 (1.23–3.33)	
Time-updated data				
Current method of family planning[f]				
Nothing	50 (31.1)	143 (31.4)	1	.650
Oral pill	29 (18.0)	84 (18.5)	1.04 (.58–1.86)	
Injection	45 (28.0)	100 (22.0)	1.30 (.77–2.17)	
Condom	30 (18.6)	103 (22.6)	0.83 (.48–1.43)	
Other (eg, traditional/calendar)	7 (4.4)	25 (5.5)	0.93 (.34–2.57)	
Condom use at last sex[g]				
No	87 (55.4)	268 (60.1)	1	.439
Yes	70 (44.6)	178 (39.9)	1.16 (.79–1.71)	
Transactional sex[h]				
No	85 (53.1)	290 (63.7)	1	.002
Yes	75 (46.9)	165 (36.3)	2.18 (.37–.98)	
Partners in the last 3 mo				
None/1	94 (58.8)	298 (65.5)	1	.148[a]
2–9	39 (24.4)	89 (19.6)	1.50 (.91–2.47)	
≥10	18 (11.3)	54 (11.9)	1.30 (.58–2.93)	
Do not remember	9 (5.6)	14 (3.1)	2.52 (.90–7.00)	

Table 2 continued.

Characteristic	Cases, No. (%) (n = 161)	Controls, No. (%) (n = 464)	Age-Adjusted OR (95% CI)	*P* Value
STI test results at the s0 and s − 1 visits				
C. trachomatis				
Negative at both visits	133 (82.6)	431 (92.9)	1	<.001
Positive at ≥1 visit	28 (17.4)	33 (7.1)	2.76 (1.57–4.87)	
N. gonorrhoeae				
Negative at both visits	130 (80.8)	426 (91.8)	1	<.001
Positive at ≥1 visit	31 (19.3)	38 (8.2)	2.58 (1.51–4.41)	
HSV-2[i]				
Negative at both visits	15 (9.4)	70 (15.2)	1	.022
Positive at ≥1 visit	144 (90.6)	392 (84.9)	2.00 (1.08–3.75)	

Abbreviations: CI, confidence interval; *C. trachomatis*, *Chlamydia trachomatis*; HSV-2, herpes simplex virus type 2; *N. gonorrhoeae*, *Neisseria gonorrhoeae*; OR, odds ratio; s0 visit, the visit during which HIV seroconversion was detected; s − 1 visit, the visit preceding the visit during which HIV seroconversion was detected STI, sexually transmitted infection.

[a] For linear trend. In the association with number of partners, we assume that women who stated "do not remember" had the highest number of partners.

[b] Only the Ugandan study included sex work as a category in answer to the question "What is your main source of income?"

[c] Data are no. of people living in the participant's residence.

[d] Data for 15 women (11 [2.4%] of controls and 4 [2.5%] of cases) were missing.

[e] Data are for experience of forced sex during the 3 mo before enrollment. Data for 13 women (9 [1.9%] of controls and 4 [2.5%] of cases) were missing.

[f] Data for 9 women (1.9% controls) were missing.

[g] Data for 22 women (18 [3.8%] of controls and 4 [2.5%] of cases) were missing.

[h] Data are for experience of transactional sex during the 3 mo before enrollment. Data for 10 women (1 case [<1%] and 9 controls [2%]) were missing.

[i] Data for 4 women (2 cases [1%] and 2 controls [<1%]) were missing.

Additional analyses of HR-HPV and LR-HPV types, analyses of nonavalent vaccine types (Table 3), and analyses restricted to the 87% of participants with s − 1 samples collected ≤6 months before HIV seroconversion (Supplementary Table 2) did not show notably different results.

HPV Clearance or Persistence and HIV Acquisition

A total of 119 cases and 323 controls had data from at least 2 time points (groups B–D in Figure 1) and were included in the analysis of the association of HPV clearance and/or persistence with HIV acquisition. Among these women, 42% had evidence of clearance of an HPV genotype irrespective of the status of other genotype-specific infections (the "any clearance" group), 10% had evidence of 6-month persistence with an HPV genotype only (with no evidence of clearance, with/without acquisition of a different genotype), and 13% had evidence of acquisition of an HPV genotype only (with

Table 3. Associations Between Human Papillomavirus (HPV) Infection at the Visit Preceding the First Detection of Human Immunodeficiency Virus (HIV) Seroconversion (the s − 1 Visit) and Subsequent HIV Acquisition Among Women With a Valid HPV Test Result at the s − 1 Visit

HPV Infection Status at s − 1	Cases, No. (%) (n = 161)	Controls, No. (%) (n = 464)	Age-Adjusted Analysis		Adjusted Analysis 1[a]		Adjusted Analysis 2[b]	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Any type								
No infection	78 (48.5)	239 (51.5)	1	.783	1	.923	1	.926
Any HPV infection	83 (51.6)	225 (48.5)	1.06 (.72–1.56)		1.02 (.68–1.53)		1.02 (.66–1.57)	
Nonavalent vaccine types								
No HPV infection	78 (48.5)	239 (51.5)	1	.867	1	.875	1	.901
Nonavalent vaccine–type HPV infection	38 (23.6)	103 (22.2)	0.99 (.61–1.60)		0.95 (.57–1.56)		0.95 (.56–1.61)	
Other HPV infection	45 (28.0)	122 (26.3)	1.12 (.71–1.75)		1.09 (.68–1.75)		1.08 (.66–1.78)	
HR/LR-HPV infection								
No HPV infection	78 (48.5)	239 (51.5)	1	.667	1	.738	1	.658
HR-HPV infection only	27 (16.8)	70 (15.1)	1.08 (.63–1.85)		1.07 (.60–1.89)		1.15 (.63–2.08)	
LR-HPV infection only	33 (20.5)	83 (17.9)	1.26 (.75–2.12)		1.19 (.69–2.06)		1.17 (.66–2.08)	
HR/LR-HPV coinfection	23 (14.3)	72 (15.5)	0.85 (.48–1.48)		0.82 (.45–1.47)		0.78 (.43–1.44)	

Abbreviations: CI, confidence interval; HR, high risk; LR, low risk; OR, odds ratio.

[a] Data are from 160 cases and 455 controls with available data and were adjusted for variables that influenced the effect estimate of the association between any HPV at s1 and HIV (ie, age group, alcohol consumption at enrollment, and transactional sex in the 3 months prior to first detection of HIV [time-updated variable]).

[b] Data are from 158 cases and 454 controls with available data and were adjusted for the same variables as for adjusted analysis 1, as well as for the time-updated sexually transmitted infection variables *Chlamydia trachomatis* detection, *Neisseria gonorrhea* detection, and herpes simplex virus type 2 (HSV-2) detection. Women were classified as positive for *C. trachomatis*, *N. gonorrhea*, or HSV-2 if they had results for tests performed at the s0 and/or s − 1 visits and if the result from at least 1 visit was positive.

Table 4. Associations of Human Papillomavirus (HPV) Persistence, Clearance, and Acquisition With Subsequent Human Immunodeficiency Virus (HIV) Infection Among Women Who Had Valid HPV Test Results From at Least 2 Time Points

HPV Persistence, Clearance, Acquisition Prior to HIV Seroconversion[a]	Cases, No. (%) (n = 119)	Controls, No. (%) (n = 323)	Age-Adjusted Analysis		Adjusted Analysis 1[b]		Adjusted Analysis 2[c]	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Among all women with >1 valid result (at s0, s − 1, or s − 2)								
Uninfected	37 (31.1)	118 (36.5)	1	.771	1	0.765	1	.685
Any HPV clearance	53 (44.5)	134 (41.5)	1.17 (.68–2.00)		1.08 (.61–1.89)		0.85 (.46–1.55)	
HPV persistence for 6 mo	10 (8.4)	33 (10.2)	0.97 (.41–2.28)		0.94 (.39–2.27)		0.93 (.37–2.29)	
HPV acquisition only	19 (16.0)	38 (11.8)	1.42 (.68–2.95)		1.44 (.68–3.04)		1.33 (.61–2.90)	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Women who remained HPV negative at all available time points were classified as uninfected. Women with evidence of any HPV clearance, defined as a genotype-specific positive test result followed by a genotype-specific negative result, regardless of concurrent HPV persistence or acquisition, were classified as having any HPV clearance. Women with at least 2 genotype-specific positive test results at least 6 mo apart, with or without evidence of acquisition of other genotypes, were classified as having HPV persistence for 6 mo. Women who only had a genotype-specific negative test result followed by a positive result for the same genotype at a later time point, with no evidence of persistence or clearance of other genotypes, were classified as having HPV acquisition only.

[b] Data are for 118 cases and 319 controls with available data and are adjusted for age group, alcohol consumption at enrollment as a linear variable, and transactional sex in the 3 months before the visit when HIV was first detected (ie, the same model as used for the analysis of the effect of prevalent HPV in Table 3; all other covariates were checked, but no other residual confounding was found).

[c] Data are for 117 cases and 319 controls with available data and are adjusted for age, alcohol consumption at enrollment as a linear variable, transactional sex, and *Chlamydia trachomatis* and herpes simplex virus type 2 detection at time of or the visit before the first visit when HIV was detected. *Neisseria gonorrhea* detection was removed from the model to reduce the number of parameters, as it did not affect the adjusted OR.

no concurrent clearance or persistence; Table 4). Among the 237 women with HPV data from an s − 2 visit, 94% had a s − 2 cervical sample collected at or within 12 months prior to the s0 visit.

Adjusted analyses based on data from all available time points did not show evidence of an association between the clearance, persistence, or acquisition of HPV infection and HIV acquisition (Table 4). Additional analyses restricted to s − 2 and s − 1 time points and excluding data from the s0 visit, when HIV infection could have influenced HPV infection, yielded somewhat larger effect estimates for all associations between HPV and HIV. However, CIs were wide, and none of the results were statistically significant (Supplementary Table 3).

DISCUSSION

In these cohorts of Tanzanian and Ugandan women, there was no evidence of an association between HPV infection, clearance, persistence, or acquisition and the odds of HIV acquisition. These results stand in contrast to other observational studies in high-risk women, which found a 2-fold increased risk of HIV acquisition in those who were HPV positive [23]. There is a plausible mechanism by which HPV infection could increase the risk of HIV acquisition through mechanical or immunological changes in the cervix [20–22]. There is strong evidence of cofactor effects of other STIs on HIV transmission [39–46]. We sought to confirm the findings of previous studies and add to limited data on HPV clearance and subsequent HIV acquisition, but we were unable to provide evidence in our study populations for such association.

Strengths of our study include its size; with 161 cases and 464 controls, our study is the largest to date. In previous studies, the number of HIV seroconverters ranged from 4 to 145 women [24–26, 28, 47]. The original cohort studies used for our investigation had high retention rates, and the characteristics of cases and controls were very similar. Cases and controls were selected from the same populations and matched to account for different study sites and designs and for individuals' adherence to study procedures. A sensitivity analysis showed that results did not differ between studies using cervical swab specimens and the one study using CVL specimens to diagnose HPV infection. The risk of misclassification of HIV infection status was low, as all studies used confirmatory HIV tests.

There are a number of possible reasons why our results differ from those reported in the literature. Apart from the Ugandan women, who included self-identified sex workers, it could be considered that the remainder of the participants had a lower risk of HIV acquisition than women recruited in previous studies, some of which only recruited sex workers [24, 26]. However, >80% of both cases and controls in our study were HSV-2 seropositive. Although cases in previous studies had a similarly high HSV-2 prevalence, the prevalence in controls was significantly lower in previous studies [27, 47]. Interactions between HPV, other sexually transmitted pathogens, and the cervical-vaginal microbiome are unclear; however, the effect of STIs on HIV acquisition may diminish the relative effect of HPV. External quality control results from the ICO laboratory indicated fair agreement in the detection of HPV genotypes; nondifferential misclassification of HPV infection may have diluted the measured effect of HPV on HIV.

Across all exposure variables investigated, there was little evidence of confounding. No information on the relative risk status of the participants' sex partners was available and missing data precluded controlling for *T. vaginalis* infection, mobility, vaginal cleansing practices, and the presence of genital warts.

However, when analyzing the available data on these variables, there were no significant associations with HIV status. Cases and controls were well balanced with regard to baseline STIs; however, residual confounding related to differences in sexual behavior cannot be excluded. The numbers of participants with clearance and 6-month persistence were small, and CIs were wide; the existence of a moderate effect of HPV on HIV acquisition cannot be ruled out.

Our study used samples that had been stored in freezers for 3–9 years. Samples that have been embedded in paraffin show good reproducibility [48, 49]; however, the durability of DNA in frozen swab aliquots or CVL specimens after long-term storage is undocumented. There is some evidence that detection of β-globin decreases over time, leading to a greater number of faint/invalid results and, therefore, potential misclassification of HPV infection status. The inclusion of s0 samples in our analysis could limit the temporal relevance of the analysis of clearance and persistence. Acquisition of HIV between the $s-1$ and s0 time points may have increased the probability of HPV persistence and/or new acquisition of HPV, which was then detectable at the s0 time point [17]. However, these time points have been used in the 2 previous studies analyzing the effect of HPV clearance and persistence on HIV, with a similar prevalence of clearance (around 40%) [27, 28]. When restricting our analysis to the $s-2$ and $s-1$ time points, the effect estimates were larger; however, CIs were wide, and *P* values preclude any clear conclusions. All studies of the association between HPV and HIV infection potentially suffer from inadequate methods of defining HPV infection status. More research is needed to find biological markers of newly acquired infection, latent infection, clearance, and persistence.

In conclusion, the HIV epidemic remains a serious problem in sub-Saharan Africa, which simultaneously harbors the highest burden of HPV infection in the world [4]. If previous reports are accurate and HPV infection leads to a 2-fold increase in risk of HIV acquisition, the highly effective HPV vaccines could substantially influence rates of HIV acquisition in areas of high HPV incidence. Whereas previous studies suggested that HPV infection enhances the risk of HIV acquisition, our study, based on a large data set from 5 cohorts in East Africa, could not confirm this association; more research is needed to clarify these contrasting results. Given the contradictory evidence of an association between HPV and HIV, a cluster randomized controlled trial of phased delivery of HPV vaccine with monitored HIV infection incidence may be the only way of concluding whether there is a causal relationship between HPV infection and HIV acquisition.

Supplementary Material

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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4.5 Additional information

4.5.1 The settings and procedures in the original studies

As stated in Section 4.4, Table 4.1, all five studies that contributed data to the nested case-control analysis recruited women at risk of HIV and other STIs who worked in bars, guesthouses or recreational facilities in urban and semi-urban areas of Tanzania and Uganda. All of the original studies measured HIV incidence and also incidence of selected STI, but did not include HPV testing. HIV incidence rates for these five studies by the end of each study's follow-up ranged from 2 to 4.3 per 100 person years (Table 4.5).

Consent procedures from the five studies were presented to a senior representative of the health research ethics committee at the National Institute for Medical Research, Mwanza. It was not deemed necessary to re-consent women in order to perform further testing on their cervical samples. On enrolment to their original studies, women had consented to be tested for a variety of STIs including testing at a future point after sample storage. Additional ethical clearance, aside from that obtained for the original studies, was also not deemed necessary by the investigators for the same reason.

Table 4.5 Summary of the study objectives and HIV incidence in the five studies that contributed data to the analysis of the association between HPV infection and HIV acquisition

Study	Study population	Dates	Main objective(s)	HIV incidence (/100 pyrs)
HSV2 suppressive treatment trial (Mwanza)[8]	Women working in bars/ guesthouses etc. (Aged 16-35)	2003-2007	To investigate whether daily HSV-2 therapy reduces HIV incidence in an occupational cohort of high risk women	4.27
MDP Feasibility Cohort (Mwanza)[9]	Women working in the bars, guesthouses etc. (Age >16 years)	2002-2004	To investigate HIV and other STI incidence and pilot lab procedures in preparation for a microbicidal gel trial	2.00
Women's Health Project (WHP) (Mwanza)[10]	Women working in the bars/ guesthouses etc. (Aged 18-44)	2008-2009	To provide estimates of HIV incidence and STI prevalence and incidence	3.3
EDCTP Vaccine Cohort (Moshi)[10]	Women working in the bars/ guesthouses etc. (Aged 18-44)	2009-2011	To determine risk factors for STIs and the genetic epidemiology of HIV infection and immune response	3.8
Good Health for Women, (Entebbe, Uganda)[11 12]	Self-reported female sex workers and women in entertainment (Aged ≥18)	2008-2011	To determine the epidemiology of HIV and STI in high risk Ugandan women.	3.6

4.5.2 Selection of cases and controls and sample size

There were a limited number of women who met the criteria as a case for the nested case-control analysis of the association of HPV infection and HIV incidence. As such, all the women who met *all* of the following criteria were included in the analysis as cases:

- Women who were tested for HIV and were seronegative at enrolment but seroconverted to HIV at a time point after enrolment (n=178);
- And who attended at least one study visit while they were HIV seronegative where a cervical sample was taken, within 12 months of the visit at which HIV was first detected (n=172);
- And who had at least one cervical sample in the laboratory archive that was taken within 12 months of the visit at which HIV was first detected (n=166);
- And at least one of these samples within 12 months of the visit at which HIV was first detected resulted in a valid HPV result after testing with the Roche Linear Array HPV Genotyping Assay (n=161).

The final selection of women contributing to our analysis represented 90% of all the women who seroconverted to HIV during the follow-up period of each study (161/178).

To maximise the power of the analysis, three control women were matched on study and visit attendance to each case. Controls were selected from the population of women who remained HIV negative at the time points of interest in their matched cases. Women who met of the following criteria were included in the analysis as controls:

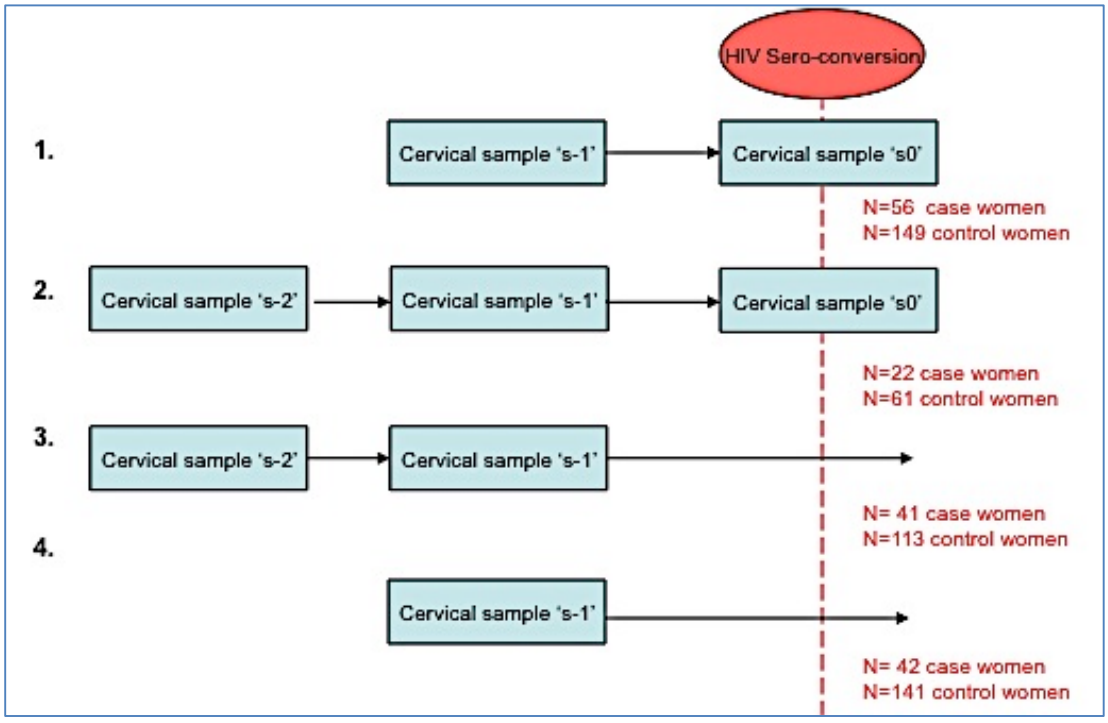
- Women who were tested for HIV and were seronegative at enrolment to the same study as their matched case and attended at least the same study visits as selected for analysis in their matched case;
- And who remained HIV seronegative at the study visit at which HIV was first detected in their matched case AND who remained HIV negative the study visit after that visit at which HIV was first detected in their matched case;
- And who had cervical samples for the study visits of interest available in the laboratory archives;
- And who had valid HPV results from those study visits of interest (n=464).

It was estimated that the resultant 161 cases, with about 3 controls per case, and 40% HPV prevalence in controls (infection with at least 1 genotype), would give us 88% power to detect an odds ratio of 1.75 for the association between any HPV infection and HIV acquisition, with an alpha of 0.05.

4.5.3 Selection and timing of samples

The number of cervical samples and the timing of cervical specimens relative to HIV seroconversion varied between women (Figure 4.2). The visit time points were defined as: 's0', the study visit at which HIV seroconversion was first detected; 's–1', the study visit before the visit at which HIV was first detected for which cervical samples were available; 's–2', the closest study visit before s-1 for which cervical samples were available.

Figure 4.2 The number of women contributing to each cervical sample combination



Women could be categorised into 4 groups, based on the number and timing of their samples (Figure 4.2). The vast majority (87%) of s-1 samples were collected at time points within 6 months or at 6 months prior to s0, and the majority of s-2 samples (88%) were collected within or equal to 9 months prior to s0 (Table 4.6). As the mechanism of the association between HPV infection and HIV is still unknown, it is unclear whether an effect, if one exists, is localised in time or could be relevant long-

term i.e. whether an HPV infection that was cleared 6 months ago still influenced susceptibility to HIV (6 months later). The proposed biological mechanism whereby HPV clearance causes weakened cell adhesion and infiltration of the cervix by a greater density of HIV target cells suggests that any effect of HPV on HIV acquisition would be relatively localised and immediate. Because of this, we included s0 samples in the analysis and made efforts to obtain s-1 and s-2 samples as close in time to s0 as possible. There are obvious limitations to the use of s0 samples in the classification of HPV infection status (Section 4.5.4).

Table 4.6 Timing of samples relative to s0 visit

Timing of s-1 sample prior to s0 (months)	**Frequency** N= 625 (161 cases, 464 controls)	**Percent (%)**	**Cumulative percent (%)**
3	344	55.04	55.04
6	201	32.16	87.20
9	53	8.48	95.68
12	19	3.04	98.72
18	8	1.28	100.00
Timing of s-2 sample prior to s0 (months)	**Frequency** N= 237 (63 cases, 174 controls)	**Percent (%)**	**Cumulative percent (%)**
6	78	32.91	32.91
9	131	55.27	88.19
12	14	5.91	94.09
15	7	2.95	97.05
18	4	1.69	98.73
27	3	1.27	100.00

4.5.4 Classification of HPV clearance, persistence, acquisition

A hierarchical analytical plan to investigate the association between HPV clearance and persistence with HIV acquisition was defined a-priori. Previous literature had identified an increased risk of HIV with recent HPV clearance and a plausible biological mechanism by which clearance could increase the host susceptibility to HIV infection[13]. On that basis, we developed the following hierarchy of HPV infection status, which was assigned to women who contributed at least 2 samples (groups 1, 2 and 3 in Figure 4.2), based on their available HPV results (Table 4.7):

- Any HPV clearance: evidence of any genotype-specific clearance irrespective of concurrent acquisition or persistence of other HPV genotypes;
- HPV persistence: HPV genotype-specific detection for 6 months or longer, with no concurrent clearance but irrespective of concurrent acquisition of other HPV genotypes;

- HPV acquisition: detection of a 'new' genotype-specific infection with no concurrent clearance or persistence of other genotypes;
- HPV negative: negative for all HPV genotypes at all study time points in the case-control set.

The inclusion of s0 samples in the analysis was justified by the hypothesis that HIV acquisition would have been too recent to have influenced HPV infection status at s0 (for 55% of women, HIV acquisition occurred within the 3 months prior to s0 visit) and s0 HPV samples would give the best indication of the HPV infection status at the time of HIV infection. This rationale for the inclusion of s0 samples is supported by evidence from a prior study, sampling at 6-month intervals, which suggested that HPV prevalence only started to rise 6 months *after* the visit at which HIV was first detected (our s0 visit) [14]. In this prior study, HPV prevalence at the visit at which HIV was first detected (our s0) was within 3% of the visit 6-months prior (our s-1 visit)[14].

We decided a-priori that the primary analysis would use all the samples available, with exploratory analyses of whether results differed when restricted to the s-2 and s-1 time points, or s-1 and s0 time points.

The likelihood of non-differential misclassification of HPV status in cases and controls due to availability (or lack) of HPV results is clearly illustrated in Table 4.7 and could have biased the results towards the null hypothesis of no association. When using only the results of s-2 and s-1 visits, multiple classifications change from clearance to uninfected, acquisition to clearance, persistence to clearance etc. and the estimates of their effect on HIV acquisition change also (Manuscript Supplementary Table 4.3).

Table 4.7 HPV genotype-specific infection patterns and classification

Time point	s–2	s–1	s0	Classification[1]
Group 1		–	–	uninfected
		+	–	clearance
		–	+	acquisition[2]
		+	+	persistence
Group 2	–	–	–	uninfected
	+	–	–	clearance †
	–	+	–	clearance†
	–	–	+	acquisition[2]
	+	+	–	clearance†
	–	+	+	persistence
	+	–	+	persistence †[3]
	+	+	+	persistence
Group 3	–	–		uninfected
	+	–		clearance
	–	+		acquisition
	+	+		persistence
Group 4		–		uninfected
		+		infected

[1] The hierarchy of classification prioritised definition of 'any HPV clearance' (irrespective of acquisition or persistence of other HPV genotypes); HPV persistence was classified as those samples with no concurrent clearance but irrespective of concurrent acquisition; HPV acquisition was classified when there was no clearance or persistence of any other genotype
[2] possibly influenced by recent HIV acquisition.
[3] This result could be persistence, reinfection, reactivation of viral latency or false negative result at s-1.
† The patterns indicated would be classified differently if either the s0 or the s–2 sample is ignored.

4.5.5 Roche Linear Array HPV genotyping assay

All cervical samples were tested for HPV DNA using the Roche Linear Array HPV Genotyping assay (Roche Diagnostics Ltd. UK) at the NIMR laboratory, Mwanza, according to an analytical plan and standard operating procedures. This test detects 13 HR HPV and 24 LR HPV types and represented the test that could detect the largest number of HPV genotypes that was commercially available at the time of the study. Detection of a large number of genotypes was considered important because there was no evidence that the previously reported association between HPV prevalence and HIV acquisition differed by high or low risk types[4 13].

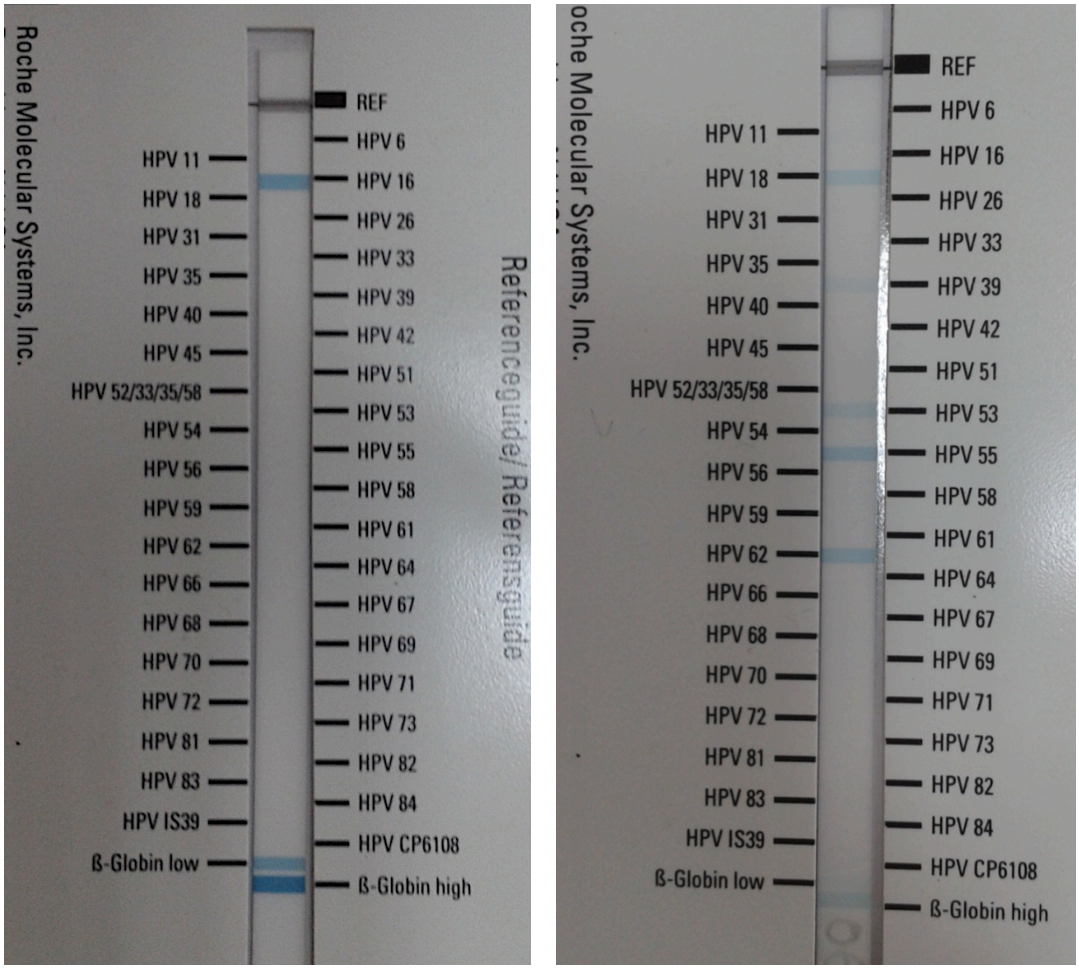
Linear array amplifies the viral DNA for the L1 viral capsid protein. The viral DNA is then detected as a specific band on a test strip (left-hand photograph in Figure 4.3). The technique is both sensitive and specific; 10-100 HPV viral genomes can be detected in 100ng of cellular DNA i.e. it is a very good method for samples with low DNA content. Results have shown high reproducibility in test-retest studies (e.g. kappa>0.9)[15 16] and good agreement with the more complex multiplex PCR assay used in a number of HPV vaccine efficacy trials, which is not commercially available[17]. Genotype-specific agreement between the linear array and multiplex assays in a controlled environment was demonstrated in a previous study as high (kappa of 0.84); agreement for the overall HPV status (positive/negative) was fair (kappa 0.62)[17].

4.5.6 Polymerase chain reaction (PCR) inhibition

The linear array assay relies on polymerase chain reaction (PCR) to amplify the viral DNA. The linear array result is classified as 'invalid' or 'inhibited' when the 2 control bands present on the strip to detect human DNA β-globin are either very faint or absent or only one is present on the test strip (right-hand photograph in Figure 4.3). Faint or absent β-globin bands mean either: 1) there was not enough biological material (human or viral) in the sample to be detected by PCR (e.g. the swab was not taken correctly or was not washed in buffer correctly); or 2) there was inhibition of PCR by factors in the sample, which prevented amplification of DNA. These inhibitors could be blood or other contaminants within the sample itself or could be chemical contamination during sample processing e.g. through inadequate washing after DNA extraction or inadequate elimination of the ethanol used for washing. Retesting the sample may indicate whether the invalid result is due to limitations in the sample or the processing technique; there is no specific test for the presence of inhibitors.

In cases of inhibition, where the β-globin bands are absent, HPV bands may or may not be visible. However, if HPV bands are visible there is no way of knowing whether there were other types present which have not been detected due to inhibition, or, if no HPV bands are visible, whether it is a truly negative result.

Figure 4.3 Example results from Roche Linear Array HPV Genotyping Assay[1]



[1] The two bands at the bottom of the test strips are the internal control bands which indicate b-globin presence i.e. verifies that DNA extraction and amplification has been possible during processing and has not been inhibited. The sample on the left is positive for HPV, we can be relatively confident it was a single genotype infection of HPV 16 due to the strong b-globin bands. The sample on the right has weak b-globin control bands indicating potentially some degree of DNA amplification inhibition, it is positive for HPV 18, 39, 53, 55, and 62. We cannot be confident that there were not other genotypes for which amplification was inhibited or for which the primers were out-competed and therefore the bands are too weak to see.

In our study, if there was enough sample volume remaining, samples with invalid results were retested from the 'raw' sample pre-DNA extraction. There was only one aliquot of swab buffer remaining in the laboratory archive for all study samples, which limited us to one retest. If there was not enough volume to retest, samples from control women with invalid HPV test results were substituted with other controls. Out of 91 invalid results, 66 had enough sample volume to retest. Twenty of all the remaining invalid samples were substituted for other controls (n=20) and 5 invalid samples from case women could not be substituted or retested and therefore were dropped from analysis along with their matched controls. On retesting, 41 of the 66

(62%) samples had detectable β-globin bands and returned a positive or negative valid result.

4.5.7 Comparability of different cervical sample types

Cells collected by cervical biopsy were initially considered to be the gold standard sample type for HPV detection. However, there is evidence that cervical samples collected with a brush or scrape gives highly comparable HPV linear array results to cervical samples collected by biopsy[18].

As such, the preferred sample types for the case control study were cervical swabs, or extracts of buffer in which cervical swabs had been washed. However, limited by the availability of the cervical swab samples in the laboratory archive, we used cervical vaginal lavage (CVL) specimens from one of the 5 studies, the HSV-2 suppressive treatment trial. Only half of the women enrolled in the HSV2 trial had both swab extracts and CVL from the same study visit still available in the laboratory archive. Swab extracts from these women were tested by linear array until 5 positive and 5 negative results were reported. The corresponding CVL samples were then tested in a small validation exercise (Table 4.8).

More HPV genotypes were detected in the CVL samples than from the extracts of cervical swabs. This is consistent with previous literature[19-21] and may be due to the CVL process sampling a wider area of the internal genitalia than a swab (since the lavage involves washing the outer cervix and vaginal walls with phosphate buffered saline). This informed the decision to use the same sample type for all case-control sets within each study to avoid introducing differential misclassification. CVL samples were used for all the cases and controls selected from the HSV2 study (34% of all cases and controls) and swab extracts were used for all other studies.

Table 4.8 Comparison of HPV linear array results using extracts of buffer in which cervical swabs were washed and cervical-vaginal lavage supernatant

Sample ID	HPV genotype result swab extract	HPV genotype result CVL
5 HPV Positive samples:		
H011721E	26,	26,59,61
H011897X	33,54	33,54
H011910U	6,18	6,18
H011989F	81,	81,
H011964C	84,	(-)
5 HPV Negative samples:		
H011745X	(-)	(-)
H011815U	(-)	45,
H011834U	(-)	INVALID*
H011886B	(-)	61,
H011999R	(-)	16,35,61

*β-Globin negative result

The clinical significance of HPV genotypes detected in CVL but not in swab extract is unclear. These HPV could indicate localised HPV invasion elsewhere in the internal genitalia and therefore be relevant in the investigation of an association with HIV, or CVL may pick up more genotypes deposited on the surface of the epithelium, which do not necessarily correspond to infections and therefore are of limited relevance to investigations of the association between HPV and HIV. Sensitivity analyses were conducted on the study results and the association between HPV and HIV did not differ by sample type in our study.

4.5.8 External quality control

The Catalan Institute of Oncology (ICO) laboratory received a random sample of 102 samples (5% of the total number of samples) including 45 CVL and 57 swab extracts. On retesting, nine samples gave invalid results at ICO and four genotypes (HPV 52, 33, 35, 58) were excluded from the external quality control analysis due to differences in reporting practices at the 2 laboratories. HPV 52 is detected in a complex primer, which presents as a positive band when any of the 4 genotypes HPV 33, 35, 52, and 58 are present and does not have an additional primer specific for HPV 52. HPV 33, 35, and 58 all have additional specific primers, which show bands on the test strip only when the specific single genotype is present. ICO record HPV 52 presence when ‘it cannot be excluded’ i.e. anytime the complex primer band

of HPV 33/35/52/58 is present. This is in contrast to the NIMR laboratory, who only report HPV 52 when certain of the presence of the genotype i.e. when the complex band of HPV 33/35/52/58 shows and none of the 3 specific primers have reacted i.e. HPV 33, 35, 58 are not present. Additionally ICO report HPV 33, 35 and 58 as '33+, 35+ and 58+ to indicate that the presence of HPV 52 cannot be ruled out.

The 93 samples and 33 genotype-specific results resulted in a total of 3069 pairs of results (Manuscript Supplementary Table 4.1). Overall percentage agreement between the labs was high: 97%; Positive percentage agreement: 68%; Negative percentage agreement: 99%; Kappa statistic for agreement between the laboratories: 0.69.

Chapter 4 additional references

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5 HPV vaccine introduction and routine healthcare services (PhD objective 3)

5.1 Preamble

Tanzania has a chronic shortage of healthcare workers and an under-resourced health system[1]. In this context, HPV vaccine was introduced through a 2-year Gavi-supported demonstration project in 2014-16 in Kilimanjaro Region. A retrospective, controlled, before-after analysis of routine healthcare data and health worker interviews was conducted to investigate whether there was evidence that a new vaccine, delivered to a new target group through outreach activities in schools, had an effect on the provision of other primary health services.

At a meeting between Dr Dafrossa Lyimo, the EPI manager within the Ministry of Health and Social Welfare, Tanzania (MOHSW), Deborah Watson-Jones and myself, to discuss HPV vaccine introduction plans in Tanzania in November 2013, Dr Lyimo raised the concern that an additional vaccine campaign could affect routine health services. I conceptualised and designed this study with advice from Deborah Watson-Jones. I calculated the sample size, designed data collection tools and interview topic guides and obtained ethics approval from the Medical Research Coordinating Committee (MRCC) of Tanzania and the research ethics committee of the LSHTM. I recruited and trained field staff and piloted and supervised data collection. Data collection was completed over 3 months, between March and May 2015, after the delivery of the final (second) dose of HPV vaccine in the first year of the demonstration project. I conducted quality control tests on the quantitative data during data collection and coded the qualitative data. I performed the analyses with the statistical help and advice from Kathy Baisley and qualitative analysis advice from Shelley Lees. I wrote the first and final drafts of the results and manuscript, which has been submitted to the International Journal of Epidemiology and Community Health.

The manuscript is formatted in accordance with the Journal of Epidemiology and Community Health requirements.

Additional information on study methods is included after the manuscript (Section 5.4).

5.2 Cover sheet: Manuscript 3

Since Thesis submission the article has been resubmitted to the journal: BMC Health Services Research. Changes as requested by peer review are included here.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Katherine E Gallagher
Principal Supervisor	Deborah Watson-Jones
Thesis Title	Evaluating human papillomavirus vaccine introduction in Tanzania and other low-resource settings

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	International Journal of Epidemiology and Community Health
Please list the paper's authors in the intended authorship order:	Katherine E. Gallagher, Tusajigwe Erio, Kathy Baisley, Shelley Lees, Deborah Watson-Jones
Stage of publication	~~Choose an item.~~ SUBMITTED

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I designed the study and data collection tools. I recruited and trained field staff and supervised data collection. I analysed data with advice. I wrote the first draft of the manuscript.

Student Signature: KEGallagher **Date:** 13/07/16

Supervisor Signature: DWatson-Jones **Date:** 13/07/16

5.3 Manuscript 3 - The impact of a human papillomavirus (HPV) vaccine campaign on routine primary health service provision and health workers in Tanzania: a controlled before and after study.

Authorship:

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ABSTRACT

Background

The burden of cervical cancer and shortage of screening services confers an urgent need for human papillomavirus (HPV) vaccination in Tanzania. However, the sustainability and impact of another new vaccine campaign in an under-resourced health system requires consideration. We aimed to determine the impact of the government's school-based HPV vaccine campaign in Kilimanjaro region on the provision of routine primary health services and staff workload.

Methods

Data on daily numbers of consultations were collected from health facility register books in 63 dispensaries and health centres in North-West Tanzania for 20 weeks in 2014. Changes in outpatient, antenatal care (ANC), family planning (FP) and immunisation service activity levels before, during and after the two HPV vaccination campaigns in 2014 in 30 facilities within Kilimanjaro region ('intervention facilities') were compared with changes in activity levels in 33 facilities in Arusha region ('controls'). Qualitative interviews were conducted with health workers in Kilimanjaro region who delivered HPV vaccination and those who remained at the facility during in-school HPV vaccine delivery to explore perceptions of workload and capacity.

Results

Health facility activity levels were low and very variable in both regions. Controlling for district, facility type, catchment population, clinical staff per 1000 catchment population and the timing of other campaigns, no evidence of a decrease in consultations at the health facility during HPV vaccination week was found across outpatient, ANC, routine immunisation and FP services. However, compared to the average week before and after the campaign, health workers reported longer working hours and patient waiting times, feeling over-stretched and performing duties outside their normal roles whilst colleagues were absent from the facility conducting the HPV vaccine campaign.

Conclusion

Qualitative interviews revealed that staff absence from the health facility is common for a number of reasons and increased the workload at the health facility. The

numbers of consultations for each service on ‘normal days’ were low and highly variable and there was no clear detrimental effect of the HPV vaccination campaign on routine health service activity.

HIGHLIGHTS BOX:

What is already known on this subject

School-based campaigns are effective in sub-Saharan Africa in reaching 9-13 year old girls with the two doses of human papillomavirus (HPV) vaccine required within a comprehensive cervical cancer prevention strategy. However, vaccine campaigns often require a significant proportion of health worker time. There are limited analyses of the impact of multi-day campaigns on the provision of routine services within under-resourced health systems, especially for HPV vaccine delivery.

What this study adds

This study analyses the impact of two separate three-day campaign periods to deliver the two doses of HPV vaccine in Tanzania in 2014 on the number of routine consultations at the health facility for outpatient, antenatal, immunisation and family planning services. Routine health service utilization was very variable throughout the 20 weeks of observed time. No impact of staff absence on the quantity of services provided at the health facility was observed. Interviews with health workers suggested that they employed strategies to mitigate the impact of staff absence during HPV vaccine campaigns on routine care. These mitigation strategies may have compromised the quality of care but this was not specifically measured.

A school-based HPV vaccine campaign required considerable human resources commitment. Further research is necessary in order to determine whether school-based HPV vaccine delivery is sustainable in Tanzania.

BACKGROUND

Resource-poor countries experience over 80% of the cervical cancer disease burden, the third most common cancer in women worldwide.[1-3] Screening services are limited across sub-Saharan Africa.[3] There are two widely licensed, safe and efficacious human papillomavirus (HPV) vaccines targeting two HPV types that cause 70% of cervical cancer, HPV 16 and 18.[4] A nonavalent vaccine targeting an additional 5 oncogenic HPV genotypes has been licensed in the USA and Europe.[4-6] HPV vaccine delivery is recommended for 9-13 year old girls in a two-dose schedule.[7] In 2012 Gavi, the Vaccine Alliance, announced funding for HPV vaccine pilot 'demonstration projects' or national programmes in low and middle income countries (LAMICs).[8] The majority of experiences in LAMICs to date have used campaign-type approaches; nurses from health facilities visit sites in their catchment area for a set number of days to deliver each dose to a target population that is often not routinely targeted for vaccines.[7, 9-14]

Introducing a multi-dose vaccine such as the HPV vaccine to a novel target population that requires out-reach activities and careful community mobilisation, could potentially stress under-resourced health systems and affect the delivery of other services.[14-16] In four studies in LAMIC examining the impact of new vaccine introductions on health systems, there was limited information on the impact on routine healthcare activities.[17] However, several recent studies have suggested that essential maternal and child health services and basic outpatient care have been affected during childhood vaccine campaigns (e.g. polio, measles) in The Gambia and Cameroon.[18-22]

In 2014, the Tanzanian Ministry of Health and Social Welfare (MoHSW) began a Gavi-supported HPV vaccine demonstration project using school-based delivery in Kilimanjaro region, northern Tanzania.[8] Tanzania had only 43.6% of the World Health Organization's (WHO) recommended number of health workers required to deliver a health service of minimum quality, with one nurse or midwife per 2,300 people and 1 doctor per 32,300 people.[23 24] Out-of-station activities by health workers have been shown to lead to task-shifting and increased work schedules for those staff remaining in the health facilities.[25] The aim of this study was to determine the impact of HPV vaccine delivery in Kilimanjaro region on the provision of routine primary health care services and health facility staff workload.

METHODS

Study design

A retrospective, controlled analysis of health facility data before, during and after the HPV vaccination campaign was completed to assess the impact of the campaign week on levels of routine service provision at the health facilities. Key informant (KI) interviews with health workers in facilities involved in HPV vaccine delivery explored the perceived impact of the vaccine introduction on the facility and workload.

The HPV vaccine demonstration project

HPV vaccine was delivered in Kilimanjaro region between 3-9th May 2014 (dose 1) and between 1-7th November 2014 (dose 2) by nurses from health facilities in primary schools within their facility catchment area. Vaccine was offered to all schoolgirls who were in grade 4 and who were aged 9 years or older. Out-of-schools girls who were aged 9 years were informed by community mobilisation activities that they were eligible to receive the vaccine in health facilities.

Study site selection

All government health facilities in Kilimanjaro region were involved in the demonstration project. Kilimanjaro region was considered the 'intervention area' and neighbouring Arusha region was the 'control area'. Of the neighbouring regions, Arusha region was chosen because it was considered to be the most similar to Kilimanjaro region in geographic and socio-economic indicators.[26]

Two districts were selected from each region to participate in the study so that intervention and control areas were similar with respect to population size and urbanisation (Table 5.1). For the quantitative analysis, 33 control and 30 intervention health facilities (government health centres or dispensaries) were randomly selected, proportional to the total number of health facilities in each study district. This ensured data from at least 30 intervention and control facilities were available. Assuming a mean of 20 visits per service per week in the control facilities and a standard deviation of 10, 30 facilities in each region conferred 80% power to detect a 36% reduction in the number of visits in the intervention clinics in a single week.

KI interviews with health workers were completed in a random sub-set of 12 of the 30 health facilities in Kilimanjaro region. Interviewees were selected on the day the health facility was visited.

Table 5.1 Districts and facilities selected for data collection

Region	Selected districts	Description and total population[1]	Total facilities[2]	No. selected facilities quantitative data collection	No. selected facilities qualitative interviews[3]
Kilimanjaro	Moshi District Council	Semi-urban 466,737	50	17 (4 Health centres, 13 dispensaries)	5
	Hai	Rural 210,533	38	13 (4 health centres, 9 dispensaries)	7
Arusha[4]	Arusha District Council	Semi-urban 323,198	27	10 (5 health centres, 5 dispensaries)	0
	Meru	Rural 268,144	55	23 (5 health centres, 18 dispensaries)	0

[1] The United Republic of Tanzania 2012 Population and Housing Census General Report. Dar Es Salaam, Tanzania: National Bureau of Statistics Ministry of Finance Dar Es Salaam & Office of the Chief Government Statistician Finance Economy and Development Planning Zanzibar, 2012.
[2] Total number of government health centres or dispensaries in each district obtained from district Ministry of Health and Social Welfare officials.
[3] The availability of interviewees determined the selection of facilities for qualitative data collection.
[4] 33 health facilities were selected in Arusha region to ensure at least 30 facilities contributed data on each service; register books were missing from 4 facilities for some services.

Data collection and analysis

Weekly counts of four routine activities were retrospectively collected from facility register books: consultations for outpatient care (OPD) among children under 5 years, Expanded Program on Immunization (EPI), first ANC visits and family planning (FP) consultations. These were well-defined activities that were routinely documented in separate register books. For each HPV vaccine dose and the equivalent calendar periods in control facilities, data were collected for 10 weeks, including the 4 weeks preceding and five weeks after the week of HPV vaccine delivery. Two data collectors entered data into Excel. The first author (KEG) validated data entry accuracy for 5% of register books. The most senior facility staff

member available provided information on number and cadre of staff, dates of training, other campaigns and the organisation of HPV vaccination teams.

The effect of the HPV vaccine campaign week on each activity indicator was assessed using negative binomial regression in Stata 13.0 (StataCorp; TX, USA), with random effects to account for the correlation of repeated observations within facilities. Models were fitted to the weekly counts of each activity with the clinic's catchment population as an offset. Separate analyses were done on the second HPV dose. Initial models contained fixed effects for region (intervention/control), week, and a region-week interaction. Adjusted models included terms for rural/urban location, type of facility, staffing levels, and whether other campaigns or training were conducted in the period of interest, all identified *a-priori* as potential confounders. We hypothesised that, if the HPV vaccine campaign had an impact on activity, the difference between the intervention and control facilities would differ by week (i.e. a significant region-week interaction), and there would be a pattern in the differences between the weeks before, during and after the campaign.

In Kilimanjaro region, 10 KI who delivered HPV vaccine at schools, and nine who remained at the facility during HPV vaccination activities were interviewed. Interview topic guides (annex 4) were translated from English into Swahili and back translated to ensure consistency of interpretation. After informed consent, a Tanzanian female research assistant conducted interviews in Swahili that included questions on health workers' perceptions of routine workload, staff capacity and the impact of the HPV vaccine delivery. Interview data were coded using Nvivo 10 software (QSR International Pty Ltd. Cardigan, UK) according to a pre-designed framework of research questions, new codes were created as they arose. The coding was conducted by KEG and reviewed by a senior social scientist, SL. Convergent mixed methods analysis gave equal weight to each component.[27-29]

Ethics

Approval to conduct the study was granted by the Tanzanian Medical Research Coordinating Committee and the ethics committee of the London School of Hygiene and Tropical Medicine. Health workers were interviewed in private, written informed consent and permission to record the interview was obtained. All data were anonymised with identification (ID) codes and stored on secure servers. Quotes are presented alongside ID codes.

RESULTS

Across all 63 facilities, there was a mean of 7 full-time clinical staff per facility (e.g. doctors, nurses, medical attendants; range 1-61). Intervention and control facilities had around 1 clinical staff per 1000 population. The mean catchment population per facility was higher in Arusha compared to Kilimanjaro (Table 5.2).

In the 30 Kilimanjaro facilities, on average, vaccination teams of 3 clinical staff took 3 days to visit 4 primary schools in their catchment area to deliver each vaccine dose (range 1-6 days; Table 5.2). The mean proportion of the workforce absent from the facility to deliver the vaccine was 50% (range 10%-100%). In 12 (40%) facilities, 70% or more of the workforce left the facility to deliver the vaccine. Administrative data of the target population of eligible girls and the number of doses delivered indicated 94.8% mean dose-2 coverage (range across facilities 70-117%; Table 5.2).

Table 5.2 Characteristics of health facilities included in the study

Selected facilities included in the study	**Control region (Arusha; n=33)**	**Intervention region (Kilimanjaro; n=30)**
Health centres, dispensaries	10, 23	8, 22
Total catchment population (adults and children)	416,606	217,813
Facility characteristics:		
Mean catchment population per facility (s.d.)	12,624 (18,423)	7,260 (4906)
Range in catchment population per facility	300 - 75000	956 - 22108
Mean number of clinical staff per facility (s.d.)	6.9 (11.1)	7.0 (5.4)
Range in total number of clinical staff per facility	1-61	2-19
Mean number of primary schools per facility (s.d.)	2.79 (1.54)	4.20 (2.93)
Range in number of primary schools per facility	1-7	1-14
Mean number of clinical doctors per facility per 1000 catchment population (s.d)	0.27 (0.43)	0.25 (0.23)
Mean number of registered nurses per facility per 1000 catchment population (s.d)	0.25 (0.49)	0.31 (0.29)
Mean number of enrolled nurses per facility per 1000 catchment population (s.d.)	0.46 (0.69)	0.36 (1.57)
Mean number of medical attendants per facility per	0.14 (0.10)	0.56 (0.43)

1000 catchment population (s.d.)		
Mean total number of clinical staff per facility per 1000 population (s.d.)	0.99 (1.38)	1.10 (0.63)
Mean number of days spent delivering HPV vaccine dose 1 (s.d; range)	NA	2.83 (1.12; 1-5)
Mean number of days spent delivering HPV vaccine dose 2 (s.d; range)	NA	2.90 (1.45; 1-6)
Mean number of staff on HPV vaccination team doses 1 and 2 (s.d; range)	NA	2.53 (1.15; 1-6)
Proportion of total clinical staff workforce involved in HPV vaccination outreach team per facility (s.d, range)	NA	0.50 (0.25; 0.12-1.2)
Mean number of girls targeted in school per facility for dose 1 (s.d; range)	NA	65.6 (50.0; 8-242)
Mean number of out of school girls targeted for HPV vaccine per facility for dose 1 (s.d; range)	NA	1.2 (3.1; 0-15)
Mean total number of girls targeted for dose 1 per facility (s.d; range)	NA	66.8 (50.2; 8-242)
Mean number of doses delivered per facility dose 1 (s.d; range)	NA	64.6 (44.3; 9-205)
Mean number of doses delivered per facility dose 2 (s.d; range)	NA	63.3 (47.5; 9-196)
Mean coverage per facility dose 1 (s.d; range)	NA	103% (28.2; 85-238)
Mean coverage per facility dose 2 (s.d; range)	NA	94.8% (9.8; 70-117%)

Data were available from every facility. NA: not applicable

Impact of HPV vaccine delivery on routine services

The average number of consultations per week for under-5 OPD, ANC, EPI and FP services varied considerably across all time points within facilities in both intervention and control sites. The under-5 OPD was the busiest service, with a range of 13-21 consultations per week across pre- and post-HPV vaccine campaign periods for both doses. There was a range of 1 to 8 first ANC consultations, 2 to 10 EPI consultations and 8-24 FP consultations per week. Mean counts of OPD, ANC, EPI and FP visits were lower in the intervention facilities than in the control during the two 10-week observation periods for both doses (Tables 5.3, 5.4).

In adjusted analyses, there was weak evidence for a difference between intervention and control facilities in the average number of weekly ANC and FP consultations before, during and after delivery of dose 1 (p values for interaction =0.09 and 0.07, respectively). However, there was no indication of a pattern over time or any evidence that the difference between intervention and control facility activity was greater during the HPV vaccine campaign week (Figure 5.1, Table 5.3).

In the periods around the second dose, there was strong evidence that the effect of 'week' on OPD, ANC and FP visits differed between the intervention and control facilities (p values for interaction=0.006, 0.002 and 0.005, respectively). However, there was no consistent pattern over time and no indication that the greatest difference in consultations was during the HPV campaign week (Figure 5.1, Table 5.4).

When comparing the number of OPD, ANC, EPI and FP consultations over time within the intervention facilities alone, accounting for facility characteristics, there was no evidence of a decrease in consultations during the HPV vaccine campaign, relative to the 4 weeks pre- or post-vaccine delivery, in either the period around dose 1 or dose 2 (Figure 5.2, Supplementary Figure 5.1). Exploratory analyses stratifying facilities into those where >50% or $\leq$50% of the workforce was absent on vaccination days found no evidence of a decrease in average activity during the campaign week in either stratum (Supplementary Figure 5.2).

Table 5.3 Impact of the HPV vaccine campaign (dose 1 delivery) on routine services.

Dose 1 weeks		Control facilities mean consults per week (s.d.)	Intervention facilities mean consults per week (s.d.)	Unadjusted RR p-value for interaction	Adjusted RR* p-value for interaction
Outpatient visits in children under 5 years				**0.240**	**0.533**
Pre-campaign	1	19.7 (16.3)	15.6 (8.77)	0.64 (0.43-0.95)	0.52 (0.34-0.81)
	2	16.2 (12.7)	12.9 (10.8)	0.58 (0.39-0.86)	0.53 (0.34-0.83)
	3	17.4 (13.2)	16.1 (10.6)	0.71 (0.48-1.05)	0.59 (0.38-0.91)
	4	13.3 (11.0)	16.4 (12.3)	0.82 (0.55-1.23)	0.70 (0.45-1.08)
Campaign	5	13.4 (10.6)	14.9 (12.6)	0.65 (0.43-0.99)	0.59 (0.38-0.93)
Post-campaign	6	15.5 (9.99)	19 (13.3)	0.79 (0.53-1.19)	0.66 (0.43-1.02)
	7	15.6 (9.84)	18.2 (13.3)	0.72 (0.48-1.09)	0.67 (0.44-1.04)
	8	19.8 (11.4)	19 (12.5)	0.63 (0.43-0.93)	0.55 (0.36-0.83)
	9	19.3 (11.1)	16.0 (9.99)	0.56 (0.37-0.84)	0.50 (0.32-0.77)
	10	15.6 (9.94)	16.7 (11.5)	0.66 (0.45-0.99)	0.58 (0.38-0.88)
First antenatal care visits				**0.028**	**0.089**
Pre-campaign	1	3.49 (4.89)	2.34 (2.11)	1.09 (0.64-1.85)	0.72 (0.39-1.32)
	2	2.45 (2.82)	2.10 (2.16)	1.31 (0.76-2.26)	0.97 (0.53-1.78)
	3	3.55 (4.59)	1.90 (2.30)	0.86 (0.49-1.51)	0.60 (0.32-1.15)
	4	3.45 (6.07)	2.21 (2.40)	1.00 (0.59-1.69)	0.70 (0.37-1.31)
Campaign	5	3.07 (3.55)	1.62 (1.72)	0.84 (0.48-1.47)	0.65 (0.35-1.23)
Post-campaign	6	3.83 (3.35)	2.52 (2.64)	1.02 (0.61-1.70)	0.59 (0.32-1.07)
	7	4.17 (5.66)	1.93 (2.14)	0.70 (0.41-1.17)	0.45 (0.24-0.84)
	8	4.48 (9.12)	2.28 (2.79)	0.77 (0.46-1.29)	0.61 (0.33-1.11)
	9	4.48 (7.37)	2.17 (2.38)	0.74 (0.44-1.24)	0.54 (0.30-0.98)
	10	4.69 (9.65)	1.31 (1.61)	0.43 (0.24-0.75)	0.29 (0.15-0.57)
Routine immunisation visits				**0.399**	**0.396**
Pre-campaign	1	6.97 (17.39)	2.87 (3.26)	1.08 (0.69- 1.70)	0.94 (0.55-1.60)
	2	5.73 (14.8)	1.80 (1.61)	0.84 (0.51-1.37)	0.70 (0.39-1.25)
	3	10.1 (25.4)	2.73 (2.38)	0.75 (0.48-1.15)	0.68 (0.41-1.12)
	4	7.93 (23.6)	2.03 (1.99)	0.72 (0.44-1.19)	0.49 (0.27-0.89)
Campaign	5	7.93 (24.0)	2.30 (2.63)	0.67 (0.41-1.09)	0.64 (0.37-1.11)
Post-campaign	6	7.50 (20.6)	3.03 (3.07)	1.01 (0.65-1.59)	0.83 (0.49-1.40)
	7	7.37 (21.6)	2.47 (2.69)	0.80 (0.50-1.28)	0.73 (0.42-1.25)
	8	8.23 (22.3)	3.40 (2.37)	1.06 (0.69-1.62)	0.95 (0.57-1.58)
	9	6.83 (19.2)	2.10 (1.83)	0.82 (0.52-1.32)	0.71 (0.41-1.22)
	10	7.30 (22.7)	3.03 (2.83)	1.06 (0.67-1.66)	0.95 (0.56-1.62)
Family planning consultations				**0.386**	**0.074**
Pre-campaign	1	14.5 (20.5)	8.43 (5.74)	0.86 (0.60-1.25)	0.40 (0.25-0.62)
	2	11.9 (12.8)	9.60 (6.20)	1.15 (0.79-1.67)	0.49 (0.31-0.78)
	3	12.1 (14.0)	11.2 (10.8)	1.33 (0.91-1.94)	0.64 (0.41-0.99)
	4	11.3 (10.1)	10.1 (9.34)	1.15 (0.781.70)	0.49 (0.31-0.77)
Campaign	5	14.6 (18.7)	11.4 (15.9)	1.01 (0.69-1.48)	0.48 (0.31-0.74)
Post-campaign	6	23.8 (59. 9)	21.3 (24.3)	1.33 (0.93-1.89)	0.75 (0.49-1.15)
	7	13.5 (27.3)	12.1 (13.8)	1.24 (0.85-1.81)	0.62 (0.40-0.97)
	8	15.7 (19.2)	12.2 (13.0)	0.94 (0.66-1.36)	0.44 (0.29-0.69)
	9	13.4 (13.9)	11.6 (10.5)	1.20 (0.82-1.76)	0.54 (0.34-0.85)
	10	17.7 (21.3)	11.5 (11.0)	1.00 (0.69-1.45)	0.42 (0.27-0.65)

* RR: the ratio in the mean number of consultations for each service in the intervention and control facilities in each week, adjusted for district, facility type (dispensary or health center), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns. P-values for interaction test the hypothesis that the effect of 'week' on activity (counts of consultations) differs between the intervention and control facilities i.e. the campaign week (week 5) has an effect on activity in intervention facilities but not on control facilities.

Table 5.4 Impact of the HPV vaccine campaign (dose 2 delivery) on routine services.

Dose 2 weeks		Control facilities mean consults per week (s.d.)	Intervention facilities mean consults per week (s.d.)	Unadjusted RR p-value for interaction	Adjusted RR* p-value for interaction
Outpatient visits in children under 5yr				**<0.001**	**0.006**
Pre-campaign	1	19.4 (20.4)	15.3 (9.7)	1.54 (1.05-2.25)	0.59 (0.36-0.98)
	2	17.8 (15.6)	12.4 (8.70)	0.42 (0.97-2.09)	0.49 (0.30-0.82)
	3	18.7 (19.1)	12.9 (10.8)	1.51 (1.02-2.22)	0.50 (0.30-0.84)
	4	20.7 (27.1)	12.8 (11.3)	1.03 (0.70-1.52)	0.47 (0.29-0.78)
Campaign	5	15.7 (19.4)	13.0 (9.73)	1.68 (1.13-2.48)	0.75 (0.45-1.24)
Post-campaign	6	16.4 (18.2)	12.9 (10.1)	1.52 (1.03-2.24)	0.57 (0.34-0.96)
	7	17.7 (17.6)	13.8 (10.1)	1.67 (1.14-2.44)	0.59 (0.36-0.98)
	8	19.8 (14.7)	14.7 (10.5)	1.62 (1.11-2.37)	0.56 (0.34-0.92)
	9	14.9 (10.8)	16.3 (10.2)	2.64 (1.79-3.91)	0.74 (0.45-1.24)
	10	15.4 (13.1)	15.4 (9.26)	2.37 (1.60-3.51)	0.78 (0.47-1.29)
First antenatal care visits				**<0.001**	**0.002**
Pre-campaign	1	5.24 (12.2)	1.66 (1.88)	0.70 (0.41-1.18)	0.58 (0.32-1.04)
	2	4.55 (9.21)	2.10 (1.99)	0.99 (0.59-1.66)	0.72 (0.39-1.33)
	3	6.10 (19.9)	1.48 (2.01)	0.65 (0.37-1.14)	0.47 (0.25-0.91)
	4	4.86 (13.1)	1.97 (1.70)	0.93 (0.56-1.55)	0.69 (0.38-1.24)
Campaign	5	4.07 (7.43)	2.97 (3.58)	1.61 (0.97-2.66)	1.29 (0.72-2.32)
Post-campaign	6	6.77 (18.1)	2.52 (3.31)	0.86 (0.52-1.42)	0.72 (0.41-1.27)
	7	8.03 (26.8)	1.69 (2.14)	0.47 (0.27-0.81)	0.38 (0.21-0.69)
	8	8.60 (24.9)	2.17 (2.74)	0.58 (0.35-0.97)	0.53 (0.30-0.95)
	9	7.73 (26.6)	2.00 (1.89)	0.66 (0.39-1.11)	0.62 (0.35-1.10)
	10	8.37 (28.3)	1.66 (1.97)	0.51 (0.30-0.87)	0.38 (0.21-0.71)
Routine immunisation visits				**0.530**	**0.627**
Pre-campaign	1	7.19 (18.7)	1.77 (1.48)	0.76 (0.47-1.23)	0.64 (0.37-1.12)
	2	7.90 (19.5)	2.27 (2.12)	0.82 (0.51-1.31)	0.63 (0.36-1.10)
	3	8.03 (23.9)	2.37 (2.68)	0.87 (0.54-1.41)	0.67 (0.38-1.17)
	4	8.55 (17.2)	2.87 (3.14)	0.75 (0.48-1.18)	0.50 (0.29-0.85)
Campaign	5	9.10 (20.6)	2.83 (2.97)	0.90 (0.57-1.40)	0.73 (0.44-1.24)
Post-campaign	6	8.06 (19.8)	2.63 (3.43)	0.74 (0.46-1.20)	0.55 (0.31-0.97)
	7	6.77 (18.1)	1.97 (2.30)	0.82 (0.50-1.37)	0.54 (0.29-0.99)
	8	7.48 (16.6)	2.10 (2.22)	0.74 (0.46-1.18)	0.56 (0.32-0.98)
	9	4.65 (10.5)	2.40 (2.18)	1.40 (0.84-2.32)	1.03 (0.57-1.86)
	10	4.97 (7.89)	2.03 (2.61)	1.07 (0.64-1.79)	0.69 (0.37-1.27)
Family planning consultations				**<0.001**	**0.005**
Pre-campaign	1	11.9 (16.6)	12.1 (12.3)	1.25 (0.83-1.88)	0.77 (0.49-1.23)
	2	13.4 (22.5)	13.1 (13.4)	0.97 (0.65-1.45)	0.68 (0.44-1.06)
	3	10.8 (14.1)	10.8 (11.5)	1.37 (0.89-2.09)	0.73 (0.45-1.21)
	4	16.5 (21.3)	9.13 (8.63)	0.92 (0.61-1.39)	0.50 (0.32-0.79)
Campaign	5	10.5 (10.2)	9.07 (7.66)	1.32 (0.87-2.00)	0.67 (0.42-1.07)
Post-campaign	6	20.4 (22.4)	9.07 (9.46)	0.65 (0.43-0.98)	0.36 (0.22-0.60)
	7	16.4 (24.2)	31.1 (36.4)	1.89 (1.30-2.76)	0.97 (0.60-1.53)
	8	13.8 (13.9)	11.7 (10.1)	1.29 (0.86-1.93)	0.80 (0.50-1.26)
	9	19.0 (25.2)	8.93 (6.16)	0.73 (0.50-1.08)	0.45 (0.29-0.71)
	10	16.4 (17.9)	8.67 (7.67)	0.99 (0.65-1.50)	0.46 (0.29-0.74)

* RR: the ratio in the mean number of consultations for each service in the intervention and control facilities in each week, adjusted for district, facility type (dispensary or health center), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns. P-values for interaction test the hypothesis that the effect of 'week' on activity (counts of consultations) differs between the intervention and control facilities i.e. the campaign week (week 5) has an effect on activity in intervention facilities but not on control facilities.

KI interviews

The 19 KIs from 12 facilities were aged between 36 and 60 years old, with an average of 12 years working as health workers (range 1-31 years). There was overlap in different cadres' reported roles and responsibilities (Table 5.5). An enrolled nurse, training to become a registered nurse, stated:

"I perform all duties; sometimes when the doctor is not around I have to take over the doctor's duties". RV03

Eight KIs from eight facilities reported that their routine workload was manageable and described having sufficient capacity to absorb more activities since the facility had adequate staffing levels and/or a small catchment population. Three KIs from three health centres indicated a heavy workload during 'normal days' with, insufficient staff, long waiting times, no time for rest breaks and working more than routine shifts. Staff absence was only cited as an issue by two KI:

"….when another person is sick, you are all alone at the facility, overworking." RV01

"During measles campaign days we become overloaded, there is a lot of work." RV02

During HPV vaccine delivery, some journeys to schools took 2 hours. However, at schools, vaccinators could usually complete vaccination in half an hour to three hours per school, depending on the number of eligible girls. Mop-up activities increased the time that vaccinators spent away from the facility; up to four visits per school were conducted to reach girls who were initially absent from school, or refused vaccination:

"Students may dodge from school, this led to the addition of more than those two or three planned days; they went for four days" RNV06

Vaccinator KIs reported that sensitisation was more difficult and time-consuming for HPV vaccine compared to other vaccines because there was a low level of awareness about HPV and cervical cancer. However, it was clear that staff perceived the workload to deliver the HPV vaccine was less than that of other campaigns as it was a smaller target population:

"For example, for that national measles rubella campaign almost all staff were out of the facility" RNV04

Regarding the perceived impact of HPV vaccine introduction on routine activities, all nine KIs who stayed at their nine facilities during HPV vaccine activities stated that the campaign increased their workload and they had to employ strategies to cope with the staff shortage. These included task-shifting and working several hours longer each day (reported by 8 KIs), or deferring less urgent patients to the next day (1 KI). All but one KI reported that staff were not allowed to take leave during campaigns.

"We have a person for every department but sometimes you find that two or three departments were attended by only a single person [during HPV vaccine delivery]. Sometimes you can be tired but just work because there is no way out" RNV01

Four KI reported that patients had to wait substantially longer to be seen. Only one KI stated that there was no impact of HPV vaccine delivery on routine service provision, despite having to close the facility to deliver the vaccine in-schools, and attributed this to the fact that the facility had a small catchment population. No KI perceived that the HPV vaccine sensitisation activities in the community affected the uptake of other routine vaccines, or dissuaded patients from coming to the facility during the campaign week. KI reported that the accuracy of register book data did not change during the campaigns.

KI were positive about the benefits of the HPV vaccine to the community and, despite the additional workload, many wanted to expand the target age group in order to protect more women. Overall, health workers involved in HPV vaccine activities supported school-based delivery, despite the transport issues and the increased workload because they could access more girls in schools and teachers could assist in sensitisation. They believed relying on facility-based delivery would lead to children absconding, or the distance between the facility and household being a barrier to vaccination.

Table 5.5 Key informant designation

Reported designation	HPV vaccinators	Non-vaccinators	Reported roles and responsibilities
Doctor	1	2	Supervision of all services and cleanliness, general administration of the facility, minor operations, referrals. Management of outpatient and reproductive and child health care.
Matron	0	1	Coordination of facility activities and colleagues, in-patient and out-patient care, MCH duties.
Registered nurse	2	2	Supervision of colleagues, provision of all services including delivery care, family planning, ANC, vaccinations, education, dispensing drugs.
Midwife	1	0	MCH, reproductive health.
Enrolled nurse	1	1	Vaccinations, under-5 outpatient services, dispensary, health education, MCH services, family planning, and outreach.
Auxiliary nurse	1	0	Assist every department.
Medical attendant/ MCH aider	4	3	Dispense drugs, dress wounds, vaccinations, assist ANC, delivery care, under-5 outpatient care, HIV VCT, and other reproductive health care, cleaning the facility.
Total	**10**	**9**	

ANC: Antenatal care; HIV VCT: human immunodeficiency virus voluntary counselling and testing; MCH: Maternal and child health

DISCUSSION

Despite the human resource and health service constraints in Tanzania, at the current level of healthcare utilization, we found no evidence that the first year of an HPV vaccine school-based campaign in Kilimanjaro region affected the quantity of consultations for routine outpatient, ANC, EPI and FP services. A study in Rwanda also found no impact of HPV vaccine introduction on the provision of ANC services,[30] although Rwanda has a relatively well-resourced health system in comparison to the rest of the region.[12 24] There is some suggestion from our qualitative research that the quality of care provided at the facility during the HPV vaccine campaign could have

been affected, with longer patient waiting times and staff performing some tasks outside their normal responsibilities.

The school-based 'campaign' delivery approach resulted in two to three health workers, half of an average facility's workforce, leaving the facility to conduct outreach in schools for 3 days, twice in the year. The strategy led to very high vaccine coverage. Health workers mitigated the impact of staff absence on the provision of routine services at the facility, despite the general shortage of health workers. The predominant mitigation strategies were to postpone annual leave, to work longer hours and to task-shift. It was common for enrolled nurses to perform the same tasks as registered (fully trained) nurses with or without supervision; this has been reported in previous studies.[25 31]

The size of the facility catchment populations and Tanzania's crude birth rate of 38.1 births per 1000 population per year,[26] leads us to expect at least double the number of ANC appointments than the two observed per week. The low level of utilisation and concentration of patient attendance in the morning hours is consistent with existing literature and could have contributed to the lack of impact.[31 32]

The strengths of this study include the mixed methods design which allowed conclusions to be drawn with greater plausibility than would have been possible using either of the methods alone. The availability of data pre-, post-, and during the campaign and the timing of this study should have limited recall bias.[27] The data collection team observed consistent use of register books during data collection activities. Qualitative data were analysed prior to quantitative data to avoid bias in the interpretation of transcripts. A range of experiences was captured at facilities with variable staffing levels and locations.

There were several limitations to this study. The extent of an impact on the quality of care, suggested by the qualitative research, was difficult to measure retrospectively. A substantial level of health worker absenteeism on 'normal days' has been reported in Tanzania.[31] Although KIs reported a reduction in health workers during campaign days, it is unclear how significant this impact was since patterns of staff absenteeism on 'non-campaign' days were not measured. Additionally, quantitative analysis could not control for ad-hoc outreach activities which were described in qualitative interviews but had no record of dates.

We focused on four services at the clinic level. It is conceivable that HPV vaccine introduction could have affected a different selection of services at different facilities depending on the nurses' different roles. Kilimanjaro region may not be representative of the potential impact of vaccine introduction on health services nationwide since the region has a 10 per 10,000 ratio of health workers to population, compared to the national average of 7 per 10,000 and 4 per 10,000 in several regions.[23 25 33]

CONCLUSIONS

Qualitative interviews revealed that staff absence from the health facility is common for a number of reasons and increased the workload at the health facility. The numbers of consultations for each service on 'normal (non-campaign) days' were low and highly variable. We found no evidence that the absence of staff from the facility for HPV vaccine campaign activities corresponded to a decrease in the number of consultations for routine services at the health facility when compared to non-campaign days, controlling for district, facility type, catchment population, clinical staff per 1000 catchment population and the timing of other formal campaigns. Further research on the impact of campaigns on health services is still necessary in order to determine their sustainability.

DECLARATIONS

Ethics and consent to participate

Ethical approval was provided by the Research Ethics Committee of the London School of Hygiene and Tropical Medicine and the Medical Research Coordinating Committee (MRCC) of Tanzania. Health workers were interviewed in private, written informed consent and permission to record the interview was obtained. All data were anonymised with identification (ID) codes and stored on secure servers. Quotes are presented alongside ID codes.

Consent to publish

All interview participants were approached for consent to publish anonymous quotes from their interview. It was clearly explained that providing consent to publish would not affect participation in the study.

Availability of data and material

All data analysed during this study are included in this published article and its supplementary files, raw datasets analysed for this publication are available from the corresponding author upon reasonable request.

Competing interests

None declared.

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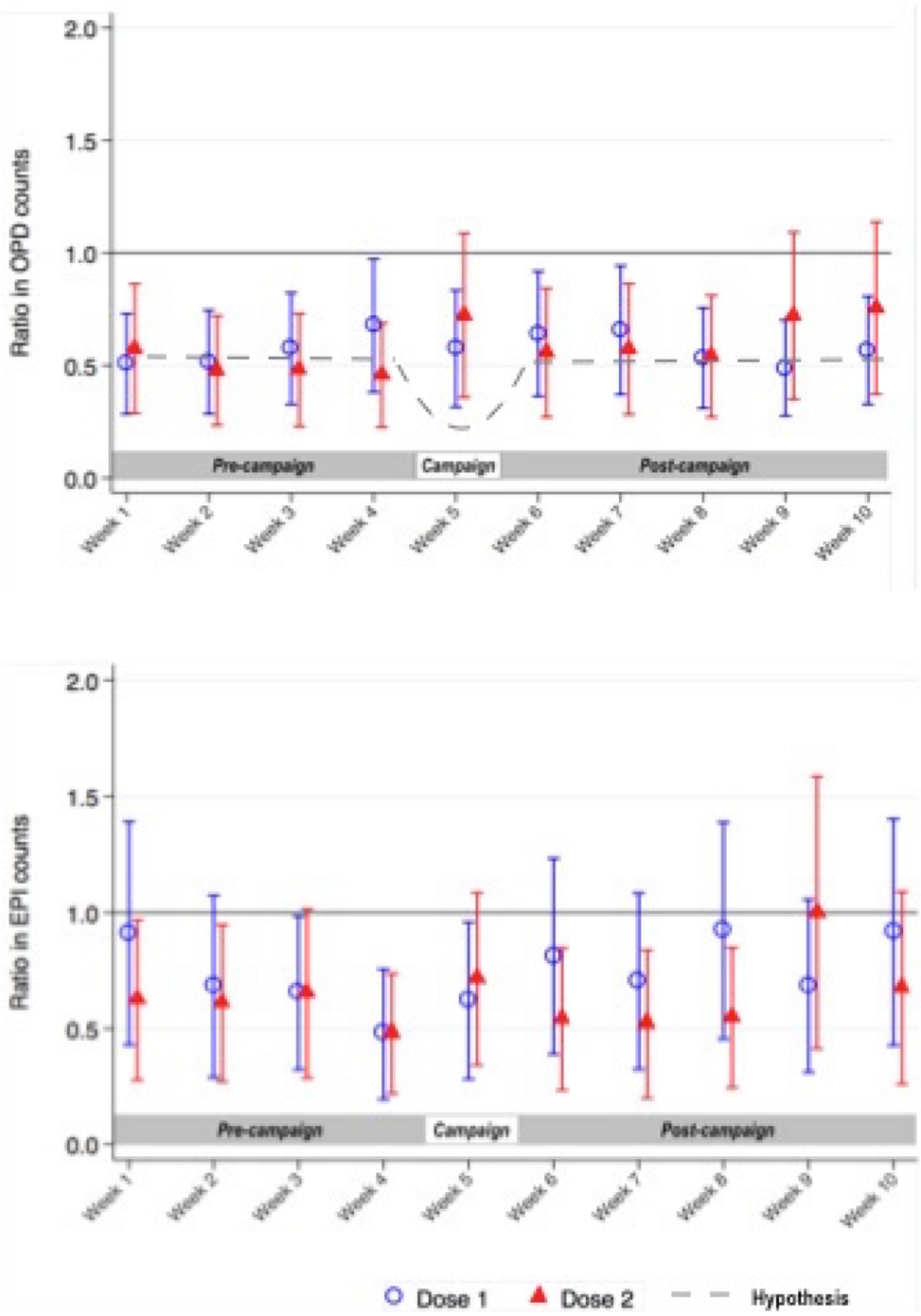
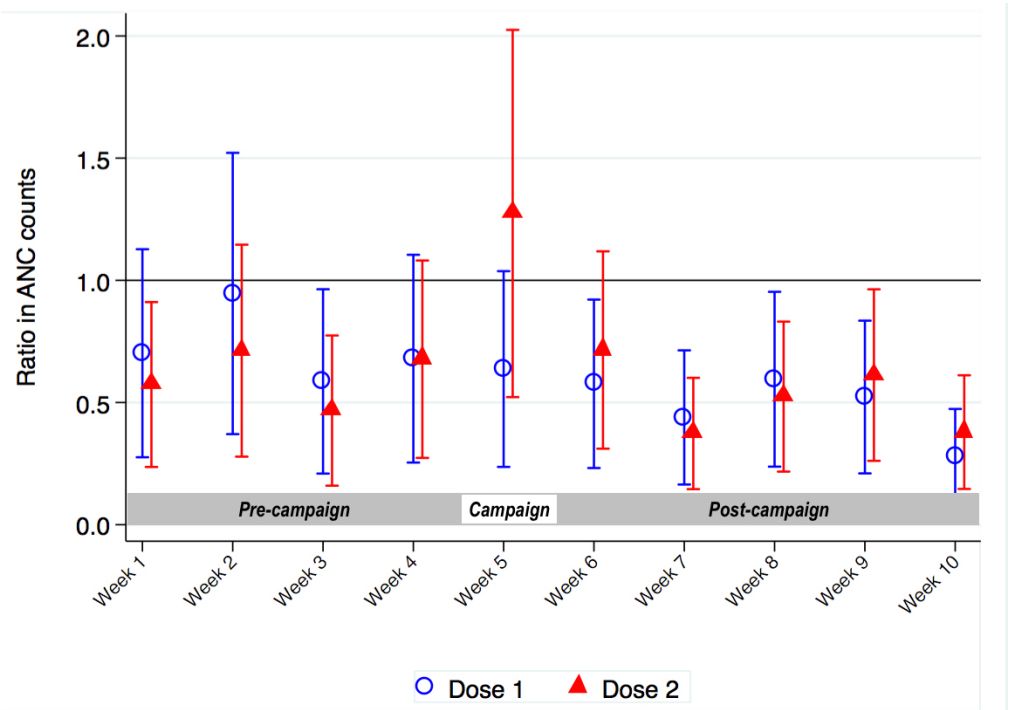
Author contributions

All authors provided essential contributions to the study design and reviewed manuscript drafts. KEG designed the study tools, supervised data collection, conducted the analyses and wrote the first draft of the article. TE interviewed key informants. KB provided essential revisions to statistical analyses. SL cross-checked qualitative analyses. DWJ helped design the study and reviewed the study tools and the manuscript.

Figure 0.1 Ratios, and 95% confidence intervals, of mean counts of the four activity indicators in intervention facilities compared with control facilities in the weeks before, during and after HPV vaccine delivery[1].

[1]Estimatated by the negative binomial regression model adjusted for district, facility type (dispensary or health centre), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns.




Ratio in ANC counts
2.0
1.5
1.0
0.5
0.0
Pre-campaign
Campaign
Post-campaign
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 1
Dose 2

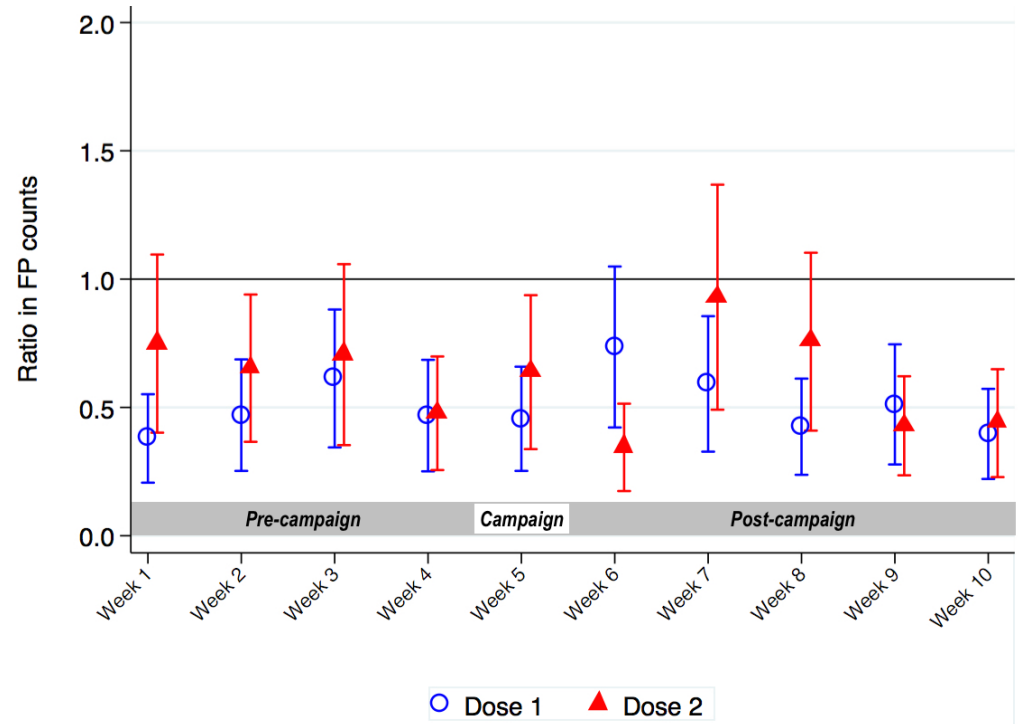
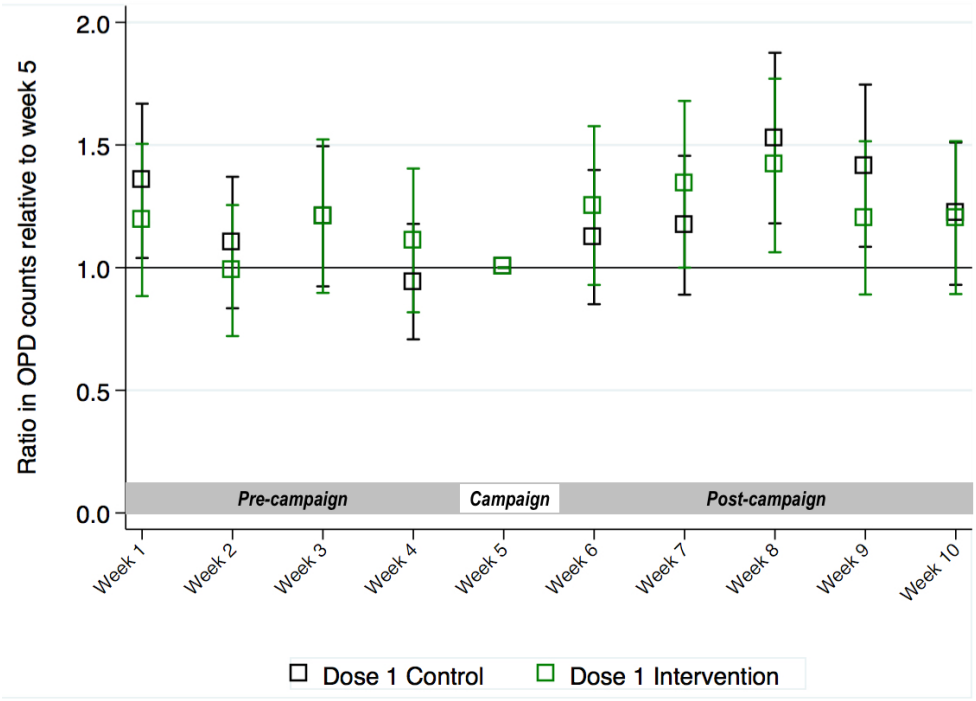
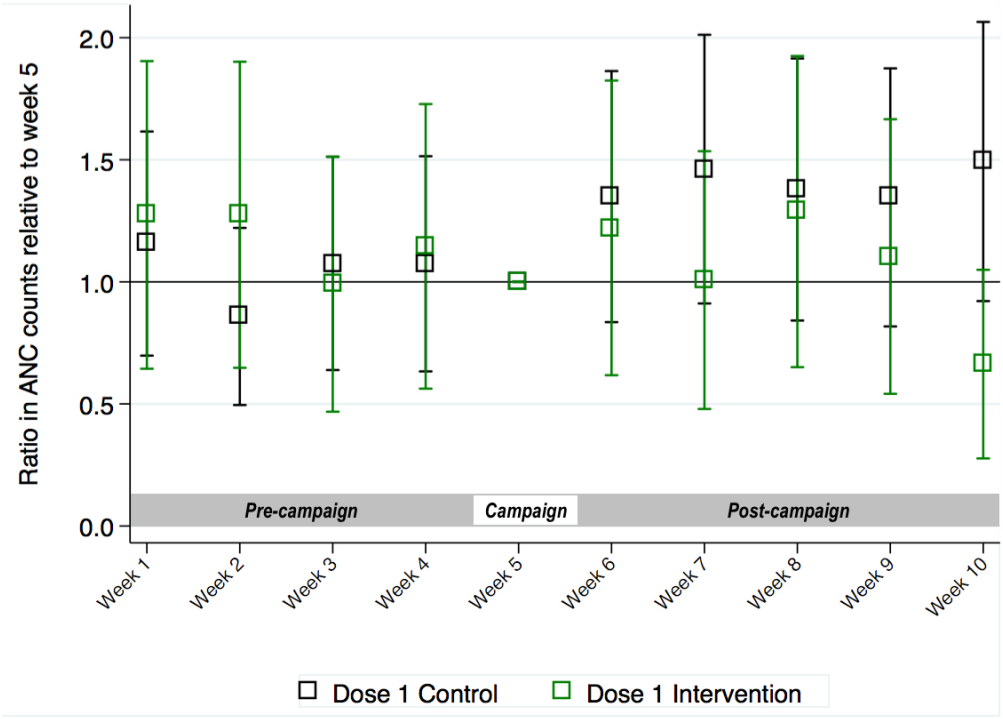
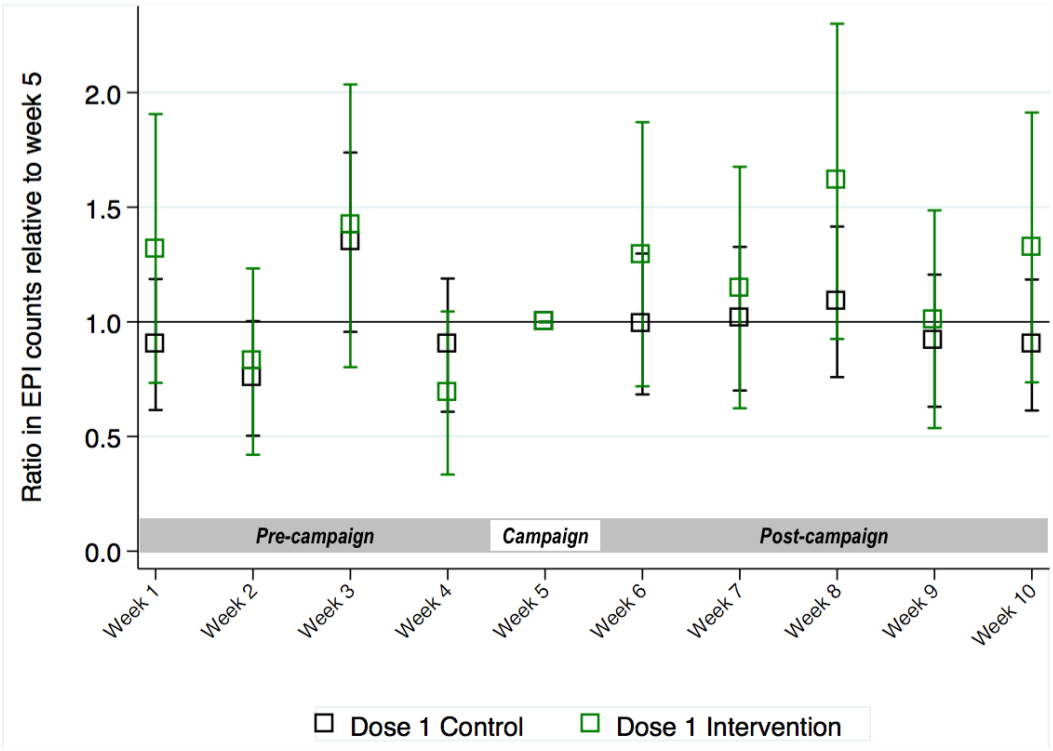

Ratio in FP counts
2.0
1.5
1.0
0.5
0.0
Pre-campaign
Campaign
Post-campaign
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 1
Dose 2

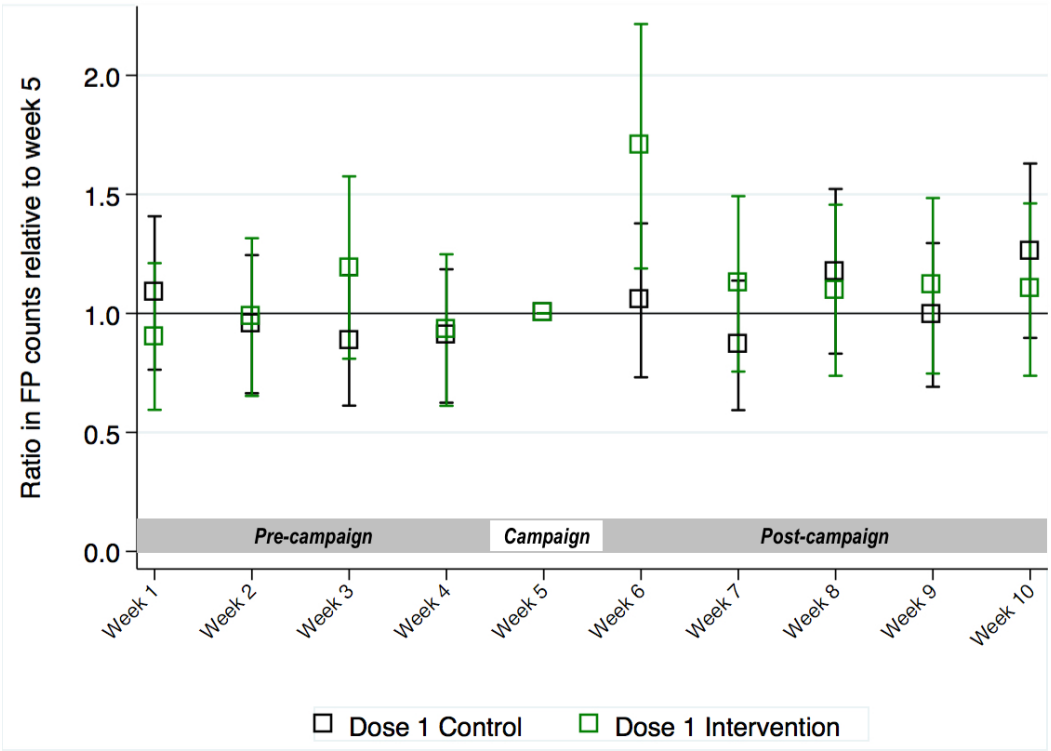
Figure 0.2 Ratios, and 95% confidence intervals, of mean counts of the four activity indicators during dose 1 delivery, comparing the weeks before and after the vaccine campaign with week 5 (HPV vaccine campaign week), or the equivalent time periods in control facilities[1]

[1]Estimatated by the negative binomial regression model adjusted for district, facility type (dispensary or health centre), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns.



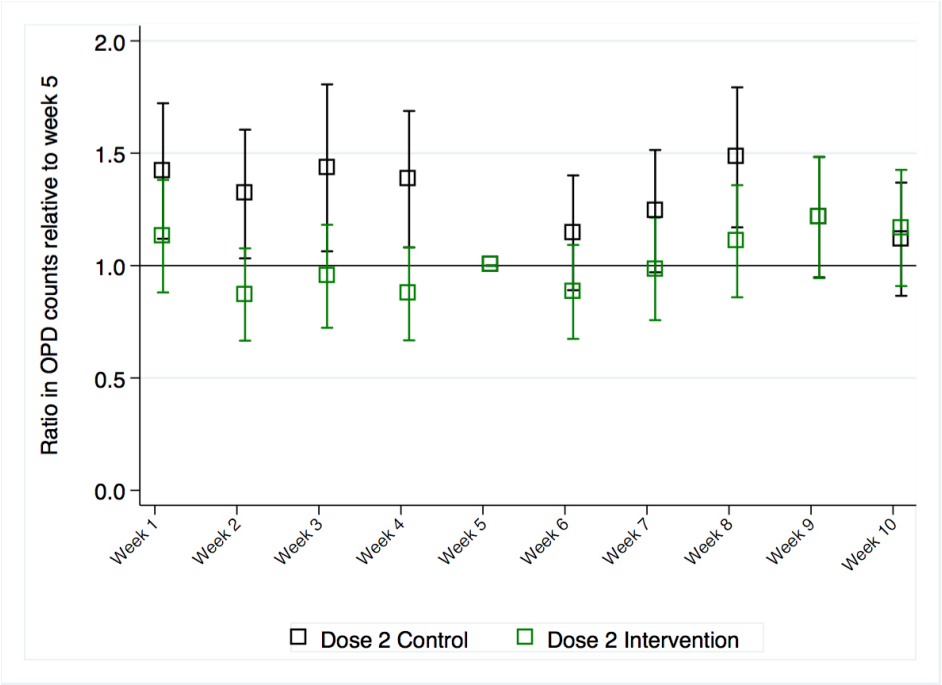


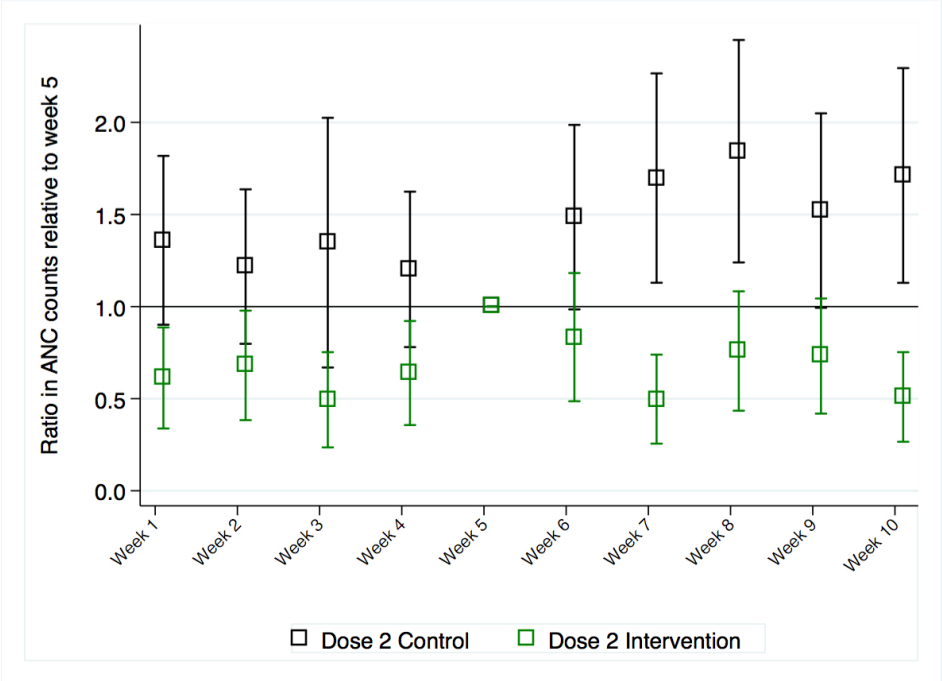

Ratio in EPI counts relative to week 5
2.0
1.5
1.0
0.5
0.0
Pre-campaign
Campaign
Post-campaign
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 1 Control
Dose 1 Intervention

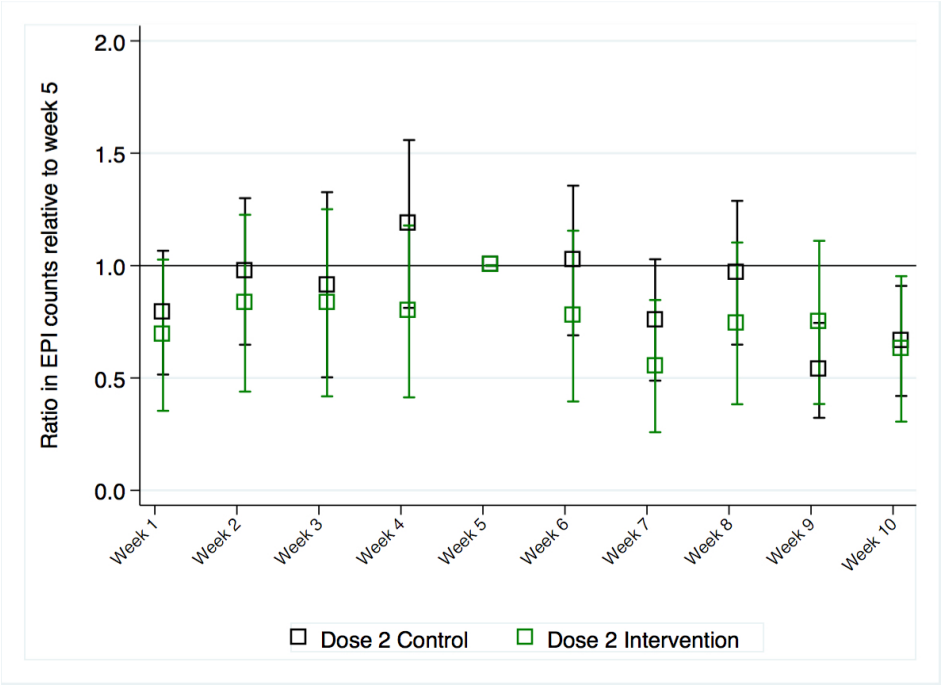

Ratio in FP counts relative to week 5
2.0
1.5
1.0
0.5
0.0
Pre-campaign
Campaign
Post-campaign
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 1 Control
Dose 1 Intervention

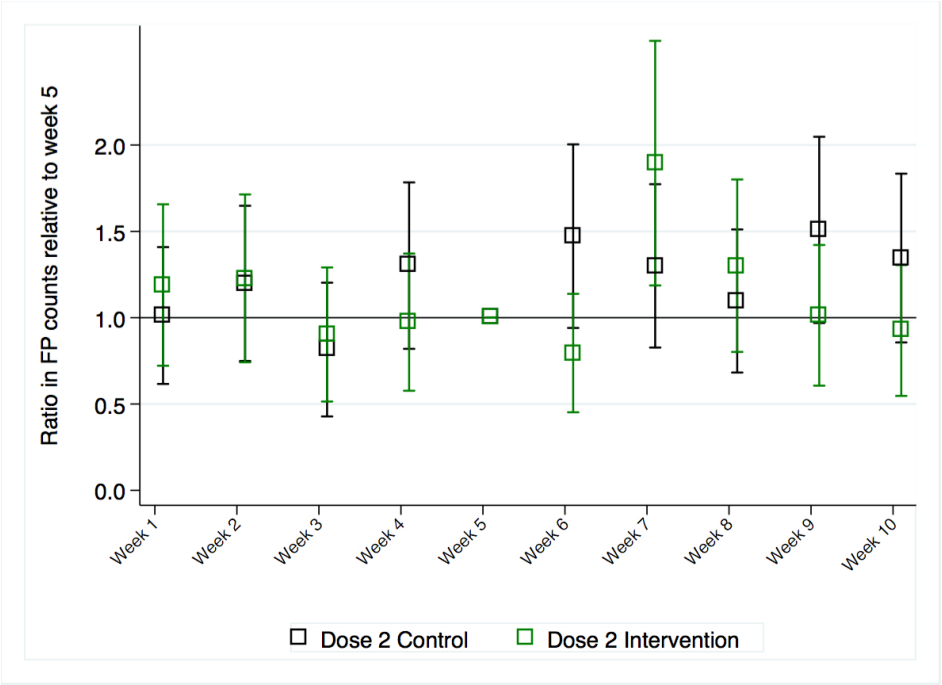
Supplementary Figure 5.1: Ratios, and 95% confidence intervals, of mean counts of the four activity indicators during dose 2 delivery, comparing the weeks before and after the vaccine campaign with week 5 (HPV vaccine campaign week), or the equivalent time periods in control facilities[1].

[1]Estimatated by the negative binomial regression model adjusted for district, facility type (dispensary or health centre), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns. OPD: outpatient care consultations for children under 5 years; ANC: antenatal care consultations; EPI: routine immunisation consultations; FP: family planning consultations.



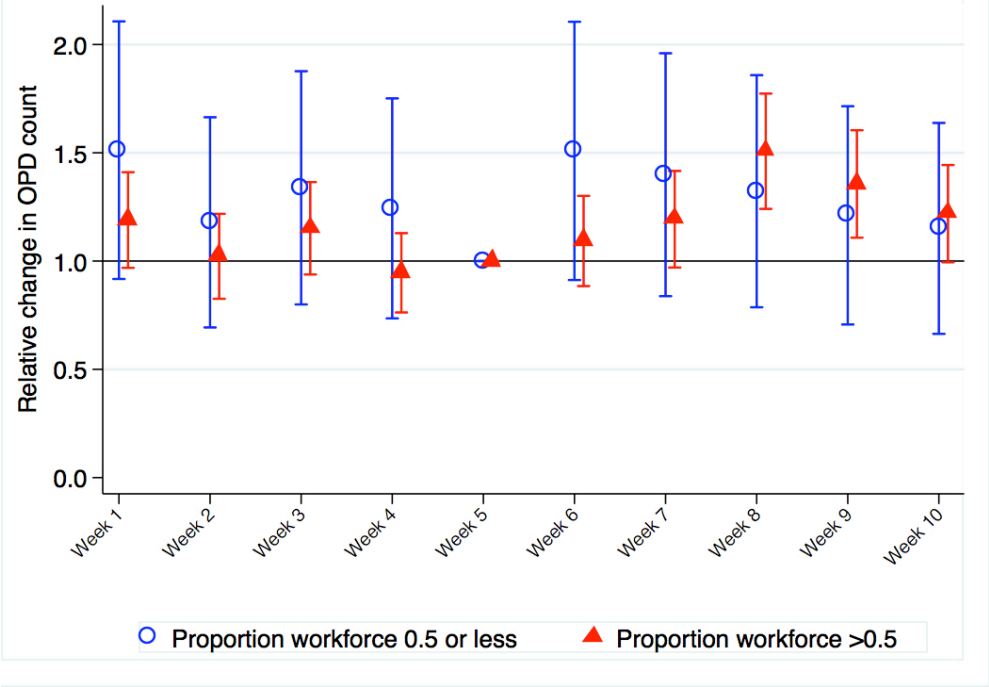


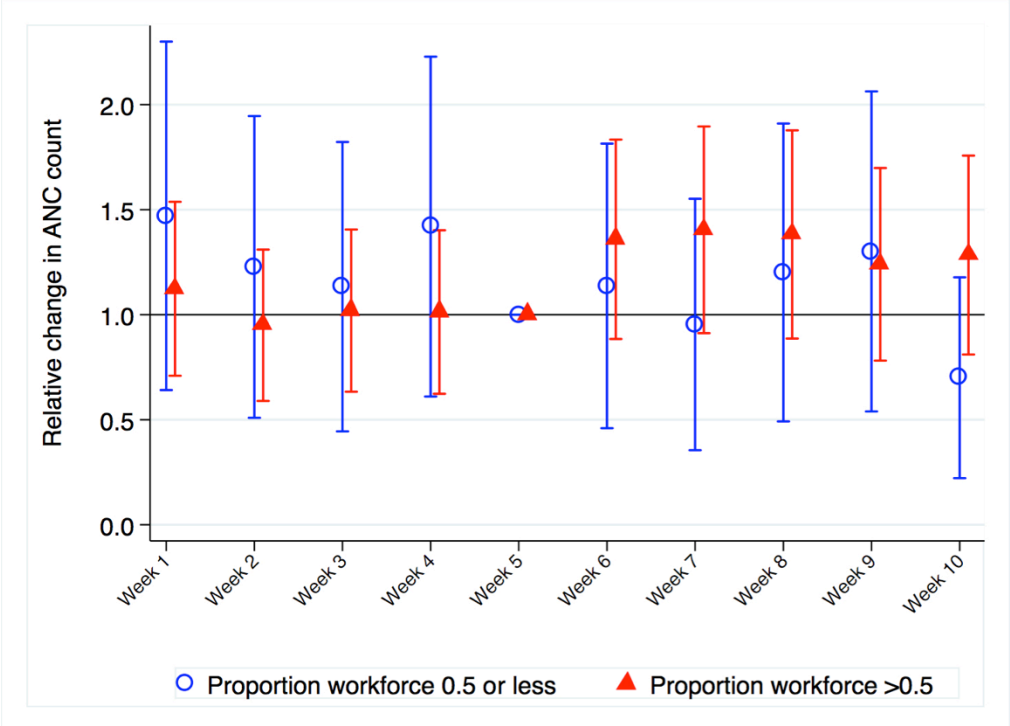

Ratio in EPI counts relative to week 5
2.0
1.5
1.0
0.5
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 2 Control
Dose 2 Intervention

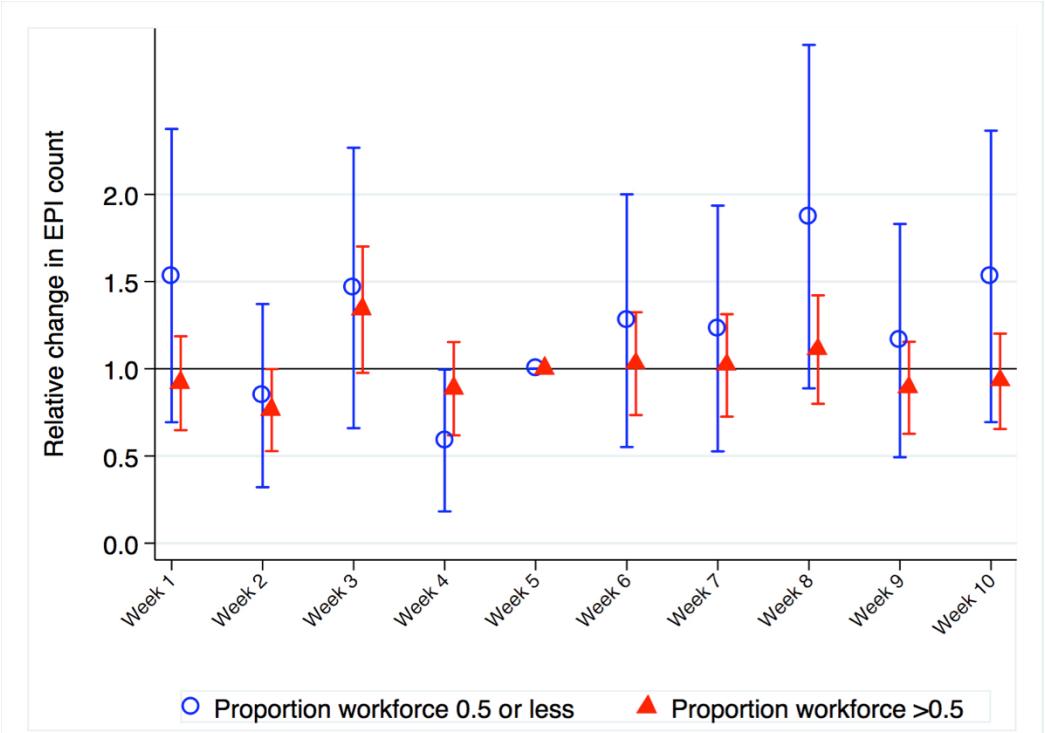

Ratio in FP counts relative to week 5
2.0
1.5
1.0
0.5
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Dose 2 Control
Dose 2 Intervention

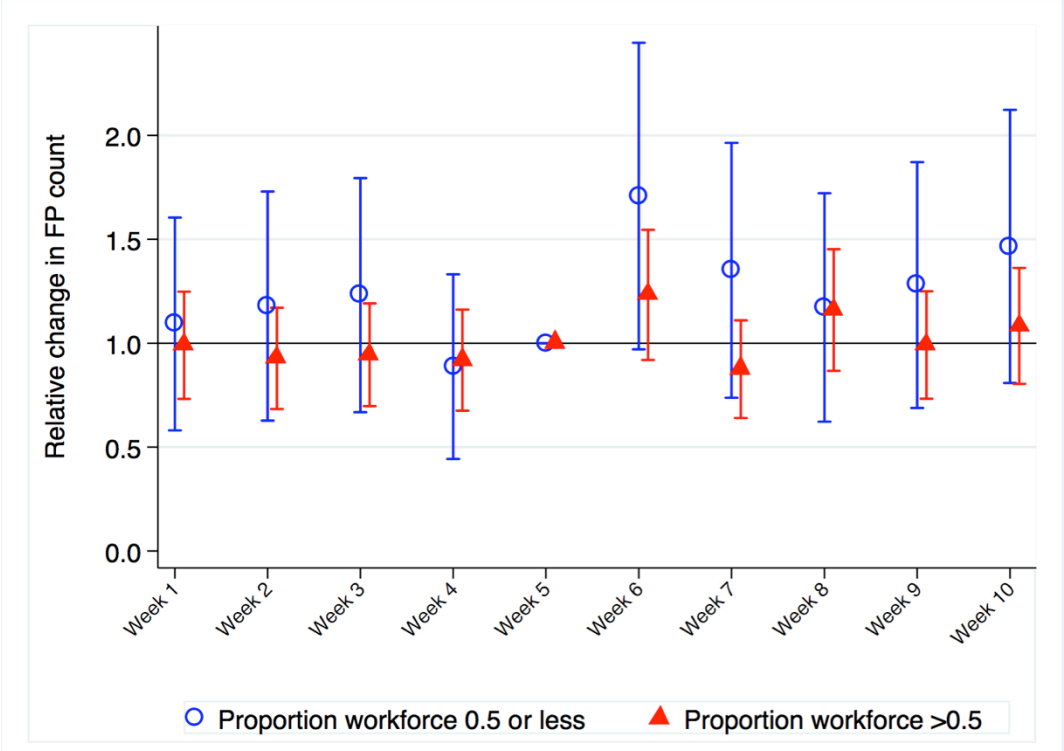
Supplementary Figure 5.2. Ratios, and 95% confidence intervals, of mean counts of the four activity indicators in intervention facilities compared with control facilities in the weeks before, during and after HPV vaccine delivery. Results are stratified by the proportion of the clinical workforce that was absent during the campaign[1].

[1]Estimatated by the negative binomial regression model adjusted for district, facility type (dispensary or health centre), catchment population, total clinical staff per 1000 catchment population per facility, timing of other campaigns. OPD: outpatient care consultations for children under 5 years; ANC: antenatal care consultations; EPI: routine immunisation consultations; FP: family planning consultations.






Relative change in EPI count
2.0
1.5
1.0
0.5
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Proportion workforce 0.5 or less
Proportion workforce >0.5


Relative change in FP count
2.0
1.5
1.0
0.5
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Proportion workforce 0.5 or less
Proportion workforce >0.5

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5.4 Additional information

5.4.1 The country context

In 2011, a team from LSHTM, working with the Mwanza Intervention Trials Unit of the National Institute for Medical Research, led a HPV vaccine demonstration project with vaccine supplied through the GARDASIL® Access Program (GAP) in Mwanza, Tanzania in order to test different HPV vaccine delivery strategies[2]. In schools, class-based vaccination attained higher coverage than an age-based strategy[3]. EPI involvement in this demonstration project was limited because of capacity in the EPI team at that time. After Gavi support for HPV vaccine was announced for Gavi-eligible countries in 2012, the Tanzanian MOHSW applied to Gavi for a two year HPV vaccine demonstration project in Kilimanjaro region, to be conducted between 2014-16[4]. This was to allow the national vaccination teams a chance to gain experience in delivering this vaccine, having been informed about lessons learnt from the Mwanza demonstration project. A full evaluation was required by Gavi and was completed by the MOHSW and technical partners after the second dose in the first year of the project in 2015, including a coverage survey[5], post-introduction evaluation (PIE)[6] and cost analysis[7]. The objective of the study presented in this thesis was to determine whether HPV vaccine delivery had an impact on routine primary healthcare provision, in districts implementing the vaccine compared to control districts.

5.4.2 Hypothesis

The hypothesis was that, in the context of an under-resourced health system, the provision of routine services at the facility would decrease when health workers were absent from the facility while delivering HPV vaccination in schools. This resulted in two main analysis questions:

- Is the difference in activity between intervention and control facilities in vaccination campaign weeks more than would be expected, accounting for variation in facility activity, service utilisation, catchment population, staffing levels etc.?
- Do health workers support the hypothesis that workload at the health facility i) increases when colleagues are absent and ii) results in fewer patients receiving care compared to other days?

5.4.3 Preparatory activity in Mwanza

I made preparatory visits to the Ilemela District Medical Office (DMO), Nyamagana hospital, Sangabuye health centre and Busisi dispensary in order to assess the availability of routine health facility data at the three typical levels of health facility within a district. Information was collected from the DMO on the contents of the standard monthly reporting forms, the registration of facilities at the district and the services available at each type of facility, e.g. hospitals, health centres and dispensaries.

Information was collected from the health facilities on the contents of the register books in distinct services, i.e. how patients were categorised and registered in different register books, what patient or care details were recorded and where. The four distinct services that formed the study's measures of routine primary healthcare activity, OPD, ANC, EPI, FP, were identified through this preparatory work.

5.4.4 Selection of analytical methods and study design

A controlled before-after analysis was selected as a robust method to investigate the effect of the vaccination activities on routine services, as randomisation of health facilities was not possible. The MOHSW had planned to deliver the vaccine to Kilimanjaro region only. Interrupted time series (ITS) analysis would have allowed time-varying confounders to be more accurately controlled, e.g. the specific days of other campaigns or outreach in the 10-week time period of interest around each dose. However, data from at least three time points during the HPV vaccination period (intervention time points) would have been needed[8]. As only two time points were available (the week of dose 1 and the week of dose 2 vaccine delivery), in discussion with my statistical advisor, it was agreed that the next best method was a controlled before-after analysis.

In the controlled before-after analysis, well-balanced characteristics of control and intervention facilities at baseline were important in order to avoid bias. A control period close in time to the intervention period was prioritised, i.e. the preceding 4 weeks before the vaccination period ('campaign') started, rather than the equivalent 'campaign week' the year before, in order to minimise the chance of large differences between intervention and control facilities[9]. The short interval between the baseline and the 'campaign weeks' achieved a good balance between the control and intervention facilities with respect to confounders such as staffing levels and catchment populations (Table 5.2; Manuscript Supplementary Tables 5.1 and 5.2).

Qualitative research was also conducted to determine if health workers' views reflected findings from the quantitative analysis of routine health facility data.

Additional data collection could have included systematic observations of health worker activity at the health facilities during vaccination time periods and 'normal weeks' and interviews with service users. However, the study timing and budget limited the scope of data collection and led to the prioritisation of the described routine data collection and health worker interviews.

5.4.5 Sample size

The sample size for the collection of routine quantitative data was calculated to estimate a simple difference in mean weekly activity between the intervention and control facilities with 80% power at the 5% significance level. It was assumed that this would be a conservative estimate of sample size as including baseline activity levels (i.e. the pre-vaccination weeks) increased the power of the analysis.

Preliminary data collected in Mwanza region was used to estimate sample size requirements due to delays in obtaining permission to operate in Kilimanjaro region. Data from three different facilities were used to estimate a mean of 30 ANC visits per month with an s.d. of 12. It was calculated that data from 28 control and 28 intervention facilities were required to detect a difference in means in intervention facilities compared to control facilities of 30%, with 80% power, at the 5% significance level. Therefore 30 control and 30 intervention facilities were approached for data *on each service*.

The number of qualitative interviews was determined based on evidence suggesting that ten in each group would be sufficient to achieve data saturation[10]. Interviews with 10 staff who delivered the vaccine and 10 staff who remained at the facility during vaccine delivery in schools was thought likely to reach a the point where only a limited number of new themes were likely to be exposed with additional interviews and this proved to be accurate[10].

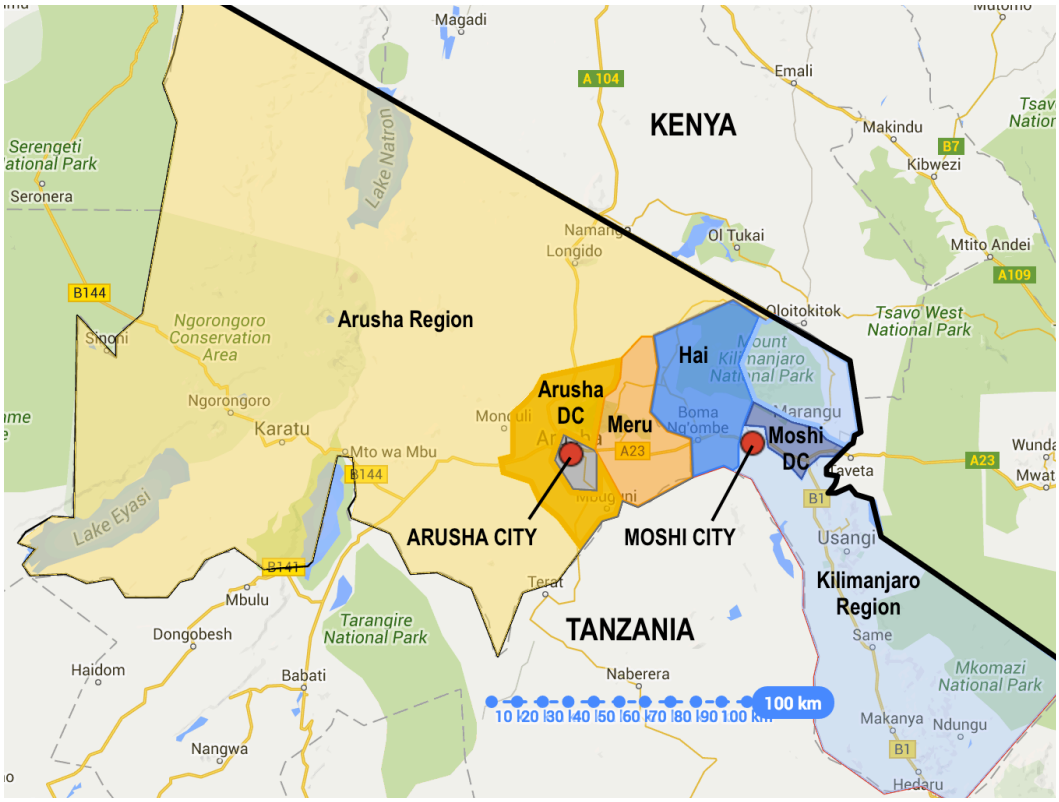
5.4.6 Region and district selection

Arusha and Kilimanjaro regions are located in northern Tanzania on the border with Kenya. The two regions encompass the foothills of Mount Kilimanjaro and have predominantly agricultural and pastoralist populations of Chaga and Masai ethnic groups respectively. The education level of the general population is just above average for Tanzania, with 29-36% of females aged 16-44 years having completed some primary education[11]. The districts

selected include urban, semi-urban and rural areas; just over 75% of the population of Tanzania lives in a rural area[11].

The selected districts within Kilimanjaro (Moshi DC and Hai) and Arusha regions (Arusha DC and Meru) were chosen to ensure the intervention study areas, in Kilimanjaro region, were similar with respect to population size, density and proximity to towns and major roads to the control study areas in Arusha region (Table 5.1; Figure 5.3).

Figure 0.3 Map of selected districts in Arusha Region (Arusha District Council and Meru district) and Kilimanjaro Region (Moshi District Council and Hai district) and regional capitals



Adapted from Google maps: https://maps.google.co.uk/ [Accessed 19 June 2016]

5.4.7 Ethical approvals and permission to conduct research

Ethical approval for the study was granted by the Medical Research Coordinating Committee (MRCC) of Tanzania and the LSHTM ethics committee (Annex 1: Ethical approvals). Letters of permission to operate in Kilimanjaro and Arusha regions were obtained from each Regional Administrative Secretary (RAS), each District Executive Director (DED), and each District Medical Office (DMO).

Confidentiality

Data collected from health facility register books were simply counts of the number of consultations in a department/section in the defined time periods; no patient-specific data were recorded. Data collected were inputted into a database on a password-protected laptop. The database was copied regularly on to a secure hard-drive that was kept in a locked cabinet with limited access.

Interview recordings and transcripts and translations were anonymised with unique identification numbers. No names were mentioned in the interview or transcripts. No identifiable information was presented in subsequent presentations, disseminations or publications of results.

The consent procedure

A trained interviewer described the study purpose and protocol to each eligible health worker in a private space either within the facility or just outside. The information on the informed consent form was read aloud by the interviewer and the participant was given a written copy in Swahili (Annex 2: Informed Consent Form). The interviewer asked the participant some questions about the consent procedure in order to ensure they understood and the participant was also given an opportunity to ask questions. All interviewees were literate.

A small payment of Tanzanian Shillings (TSH) 5,000 (equivalent to GBP 2) was made to participants after the completion of the interview in compensation for their time taken out of their daily breaks or lunchtime. This is a standard amount used in MITU studies and equates to a small percentage of a nurse's average daily salary and is below the level that would constitute undue incentive to participate in the study.

5.4.8 Selection of health facilities

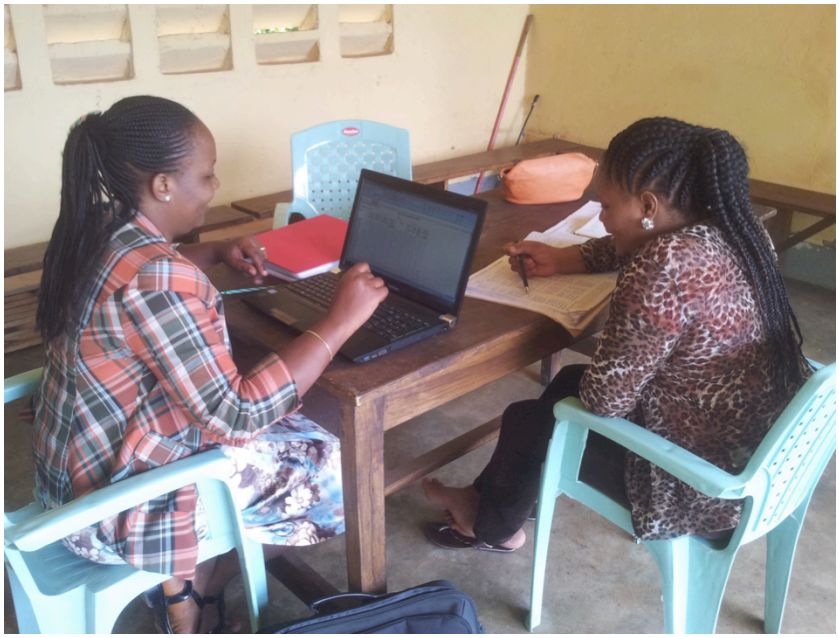
Lists of health facilities in the selected districts in Kilimanjaro and Arusha Regions were compiled from the DMOs. Facility name, urban and rural location and contact numbers were collected. In Kilimanjaro region, HPV vaccine coverage statistics were also obtained from DMOs, disaggregated by health facility. For quantitative data collection, 30 'intervention' health facilities were randomly selected from the 2 district in Kilimanjaro region alongside 30 'controls' from the 2 districts in Arusha region. All facilities registered with the DMO were registered as providing the four routine services of interest (OPD, ANC, EPI, FP). Three of the selected facilities in Arusha region had not started delivering one or two of the services of interest and therefore an additional three facilities were randomly selected to ensure data from at least 30 facilities were available for each service of interest.

For the qualitative data collection, 12 facilities in Kilimanjaro region were randomly selected to ensure that about 10 interviews with vaccinators and 10 with non-vaccinators were possible. A maximum of one vaccinator and one non-vaccinator interview was conducted at each facility. Interviews were dependent on staff availability on the day of data collection; 19 interviews were finally conducted in 12 facilities.

5.4.9 Quantitative data collection

After permission to collect data in the facility was granted, the staff member in charge of the facility on the day of data collection was then asked some questions in order to complete a full facility description form (Annex 3: Data collection forms). Routine health care data were collected from facility register books (the outpatient department, reproductive child health service (RCHS), immunisation and family planning register books), by week, for two 10-week periods across March-May and October-December 2014). The same data were collected from control facilities (Figure 5.5). The time-span, controlling for periods of other centrally organised health campaigns or HPV vaccine training, allowed an estimate of a baseline measure of activity, prior to HPV vaccine roll-out in both vaccination and control facilities.

Figure 0.4 Quantitative data collection



The two research assistants completed data collection on the four indicators over about 2 hours per facility.

5.4.10 Qualitative health-worker interviews

An experienced national graduate female qualitative interviewer accompanied the data collection team to 12 facilities in both districts in Kilimanjaro region. Qualitative interviews were designed to include topics listed as key indicators of health system workforce strength by WHO: the availability and distribution of staff, staff training and capacity, remuneration and job satisfaction, and performance and supervision[12] (see Annex 4: Interview topic guides).

Chapter 5 additional references

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6 Lessons learned from HPV vaccine demonstration projects and national programmes (PhD objective 4)

6.1 Preamble

The impact of the HPV vaccine on HPV-related sequelae depends on the success of implementation. By the first quarter of 2015, 37 LAMICs had completed at least one year of an HPV vaccine demonstration project or national programme. We conducted the first comprehensive review of the published and unpublished evaluation data from these projects and programmes and supplemented the literature with key informant interviews.

I helped to develop the proposal and budget for this study in collaboration with Deborah Watson-Jones, Scott LaMontagne, Ulla Griffiths and Helen Burchett. I coordinated study activities for the data collection, synthesis and interpretation of the findings, designed the data collection tools with input from co-investigators, obtained published and grey literature and conducted half of the key informant interviews (KII) in person or over the phone. I helped to coordinate the remaining KII. I led on data synthesis, production of the final project report and wrote the first draft of the manuscript. I also co-managed the study budget with Deborah Watson-Jones. Together with all the other co-investigators, I contributed to the drafting and review of all other project dissemination materials produced by PATH: the 4-page and 2-page summaries, the world map, the poster, the video script, and the PowerPoint slide deck. I was also a panel member on the interactive Webinar that we produced. All outputs are available at http://www.rho.org/HPVlessons/.

The manuscript is formatted in accordance with the requirements of the Bulletin of the World Health Organization.

Additional information on study methods is included after the manuscript (Section 6.4).

I have delivered **oral presentations** of this work in the following forums:

- WHO global learning meeting on human papillomavirus (HPV) vaccine introduction; Geneva, Switzerland; 10-12th November 2015.
  Oral (1 hour split equally between 3 speakers): **Lessons learnt from human papillomavirus vaccine delivery in low and middle-income countries**. Speakers: Deborah Watson-Jones, Scott LaMontagne, Kate Gallagher.

- EUROGIN; Salzburg, Austria; 15th-18th June 2016.
  Oral (7 minutes): **HPV vaccine coverage achievements in 34 low and middle-income countries 2007-2015**. Speaker: K Gallagher.
- The HPV Prevention Board; University of Antwerp, Antwerp, Belgium; 27th-28th June 2016.
  Oral (25 minutes): **HPV vaccination experience in 45 low and middle-income countries: lessons learnt**. Speaker: K Gallagher

I have delivered **poster presentations** at the following conferences:

- The 30th International Papillomavirus Conference ('HPV 2015'); September 17-21st 2015; Lisbon, Portugal. '**Lessons learnt from human papillomavirus vaccine delivery in low and middle income countries'**. Gallagher K.E., Griffiths U.K., Burchett H., Howard N., Kabakama S., Mounier-Jack S., LaMontagne D.S., Watson-Jones D.
- AORTIC 2015, 10th International Conference on Cancer in Africa; November18 – 22nd 2015; Marrakech, Morocco. '**Lessons learnt from human papillomavirus vaccine delivery in low and middle income countries'**. Gallagher K.E., Griffiths U.K., Burchett H., Howard N., Kabakama S., Mounier-Jack S., LaMontagne D.S., Watson-Jones D.

Other co-authored publications of this work include:

1) **Social mobilization, acceptability, and consent procedures for human papillomavirus vaccination in low- and middle-income countries.** Severin Kabakama[1], Katherine E Gallagher, Natasha Howard, Sandra Mounier-Jack, Helen ED Burchett, Ulla K Griffiths, Marta Feletto, D Scott LaMontagne, Deborah Watson-Jones. *BMC public health* 2016, **9**(16 (1)).
2) **The value of demonstration projects for new interventions: the case of human papillomavirus vaccine introduction in low-income and lower-middle-income countries.** *Howard N, Mounier-Jack S, Gallagher KE, et al. Human vaccines & immunotherapeutics 2016:1-3.*

6.2 Coversheet: Manuscript 4

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Student	Katherine E Gallagher
Principal Supervisor	Deborah Watson-Jones
Thesis Title	Evaluating human papillomavirus vaccine introduction in Tanzania and other low-resource settings

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	WHO Bulletin
Please list the paper's authors in the intended authorship order:	K.Gallagher, N. Howard, S. Kabakama, U. Griffiths, S. Mounier-Jack, M. Feletto, D.S. LaMontagne, H.Burchett, D. Watson-Jones
Stage of publication	~~Choose an item.~~ SUBMITTED

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I coordinated data collection. I led on data synthesis, production of the final project report and wrote the first draft of the manuscript.

Student Signature: KGallagher **Date:** 13/07/16

Supervisor Signature: DWatson-Jones **Date:** 13/07/16

6.3 Manuscript 4: Lessons learnt from human papillomavirus vaccination in low- and middle-income countries

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Abstract

Objective

To synthesise lessons learnt and determinants of success from human papillomavirus (HPV) vaccine demonstration projects and national programmes in low and middle-income countries (LAMICs).

Methods

A systematic literature review identified 1301 abstracts from five databases; after screening 41 full texts were included. Unpublished literature, including evaluation reports, was solicited from country representatives; 124 documents were received. Interviews were conducted with 27 key informants to fill data gaps in 23 countries. A data extraction tool and interview topic guide outlining key areas of inquiry were informed by World Health Organization guidelines for new vaccine introduction. Results were synthesised thematically.

Findings

Data were analysed from eight national programmes and 55 demonstration projects in 37 countries. Among demonstration projects, 29 were supported by the GARDASIL® Access Program, nine by Gavi, four by PATH and 13 by others. School-based vaccine delivery supplemented with health facility-based delivery attained higher coverage than school- or facility-only strategies. Information and evaluation of strategies to reach out-of-school girls were limited. Early engagement of teachers as partners in social mobilisation, consent, vaccination day coordination, follow-up of non-completers and adverse events was considered invaluable. Micro-planning using school/facility registers most effectively enumerated target populations; other estimates proved inaccurate, leading to vaccine under- or over-estimation. Refresher training on adverse events and safe injection procedures was usually necessary.

Conclusion

Considerable experience in HPV vaccine delivery in LAMICs is available. Lessons are generally consistent across countries and dissemination of these could improve HPV vaccine introduction.

Background

Globally, an estimated 528,000 new cervical cancer cases and 266,000 deaths occur annually [1]. Over 85% of new cervical cancer cases occur in women living in low and middle-income countries (LAMICs), who have limited access to screening services [1-4]. There are two licensed prophylactic HPV vaccines against persistent infection with HPV vaccine genotypes and high-grade cervical intraepithelial neoplasia, pre-requisites for cervical cancer development [5]. Cervarix® (GlaxoSmithKline Biologicals) targets HPV genotypes 16 and 18 and GARDASIL® (Merck & Co. Inc) targets HPV 16 and 18 as well as 6 and 11, the primary causes of genital warts [6]. As HPV is sexually transmitted, the World Health Organization (WHO) recommends targeting HPV vaccination to girls prior to sexual debut (e.g. age 9-13) because it is most efficacious in those who have not been exposed to HPV [7].

Between 2007 and 2012, several LAMICs conducted HPV demonstration projects with vaccines provided by the GARDASIL® Access Program (GAP) [8], Merck & Co., the Bill & Melinda Gates Foundation through PATH, or through other means. Demonstration projects are small-scale pilots through which experience can be gained in delivering the vaccine to what is often a novel target age group [9]. In 2012 Gavi, the Vaccine Alliance (Gavi), commenced support to demonstration projects and national introductions to increase access to HPV vaccination worldwide. The majority of demonstration projects are now Gavi-funded. National programmes may also be funded by Gavi if the country has prior experience of vaccination in the target age group and achieved over 50% vaccination coverage. By August 2015, 80 countries or territories had commenced national HPV vaccination and another 38 had completed or started HPV vaccine demonstration projects [10].

Country decision-makers face several challenges when applying for support and introducing HPV vaccine. These include selection of delivery strategy, effective communication with communities and how to maximise coverage [11, 12]. At the time of this study, no comprehensive review of results and lessons learnt from demonstration projects or early scale-up in LAMICs had been conducted. This study aimed to synthesise lessons learnt from HPV demonstration projects and national programmes in LAMICs implemented between January 2007 and January 2015 to develop recommendations for HPV vaccine delivery and accelerate scale-up of national programmes.

Methods

This cross-sectional study included a systematic literature review, a review of unpublished reports and semi-structured key informant interviews. Units of analysis were: 1) countries, 2) projects/programmes, and 3) delivery experiences; projects, programmes and delivery experiences are defined in Table 6.1.
A mapping exercise identified LAMICs that had completed at least one year of an HPV vaccine demonstration project or national programme by the end of January 2015 (n=37; Table 6.2). All experiences from low and lower-middle income countries were included. Data from upper-middle income countries were only included if they conducted a demonstration project, rather than immediate national rollout. At least another 15 LAMICs had or were planning to start Gavi-supported demonstration projects, but did not have data in time for inclusion in this study.

Systematic literature review

Five databases (Medline, Embase, Global Health, Africa-wide Information, ADOLEC) were searched systematically for published literature in December 2014. Search terms relating to HPV, vaccination or immunization were combined with country terms, with no language restrictions (Supplementary Table 6.1). For each country, searches were limited to publications from the first year of HPV vaccine experience onwards, if known, to reduce the number of articles retrieved that did not document vaccine delivery (e.g. hypothetical acceptance studies). Reference lists of identified reviews and retrieved papers were checked for missing papers. One author was contacted for an unpublished manuscript. References were screened for inclusion using set criteria (Figure 6.1).

Unpublished reports

Authors systematically searched two databases (Open Grey, ProQuest) and several websites (national Ministries of Health (MOH), WHO Global Immunization News, Pan-American Health Organization newsletters, scientific conferences on HPV) for unpublished literature through January 2015. Unpublished reports were solicited directly from country representatives and stakeholders involved in HPV projects/programmes.

Key informant interviews

Representatives from 33 of the 37 countries were approached for interview in order to fill gaps in the data in the published and unpublished literature. No significant gaps were identified in four countries; two countries were not approached due to on-going emergencies. Interviews, by phone or in-person, were sought with focal people from each HPV vaccine project/programme in a country, if more than one had been conducted. A topic guide was adapted to address identified knowledge gaps. All interviewees were assured of confidentiality and anonymity to encourage openness about experiences.

Data extraction

KG, NH, and SK extracted data during February-May 2015, using an Excel-based matrix of key areas of inquiry informed by WHO's new vaccine introduction guidelines [13]. The matrix was piloted and revised twice, with two consistency checks conducted. Data from published, unpublished and interview sources were extracted into the same matrix.

Data analysis

Country data from all sources were triangulated and analysed together in seven themes: preparation, communications, delivery, achievements, sustainability, integration and value of demonstration projects. Data were grouped by calendar year, world region and type of funder or implementer to analyse patterns.

Qualitative data were analysed thematically across data sources. Quantitative data (e.g. coverage, adverse events) were analysed descriptively to present frequencies and proportions. Reported coverage estimates were categorised as percentages because not all projects/programmes shared numerator and denominator data to enable coverage calculations.

The London School of Hygiene & Tropical Medicine Research Ethics Committee approved the study in March 2015.

Results

In total, 41 published articles, 9 conference abstracts, and 124 unpublished documents were included in the review. Unpublished documents received from country representatives and international partners from 35 of the 37 countries included: GAP final reports (n=16); Gavi post-introduction evaluations (PIEs; n=4); other PIEs (n=2); Gavi cost analyses (n=1); Gavi coverage survey (n=2); other coverage survey (n=8) and other internal reports (n=91). Additionally, 27 interviews were conducted covering experiences from 23 countries (29 demonstration projects, three national programmes). Eight country representatives invited to interview either refused to participate or did not respond.

The 37 countries that implemented HPV vaccination projects/programmes between January 2007 and January 2015 accumulated 89 years of implementation experience (Table 6.2). By January 2015, 41% of countries (n=15) had 2-3 years of experience, 38% (n=14) had one year of experience and 21% (n=8) had four or more years of experience in national programmes or multiple demonstration projects. This included eight national programmes and 55 demonstration projects. Only three projects/programmes in three countries had implemented one year of a two-dose HPV vaccine schedule by January 2015; all others implemented a three-dose schedule. HPV vaccination was free-of-charge to recipients.

Preparation

Leadership and planning

Two-thirds of projects/programmes were led by the MOH, with lead departments varying between cancer, school/sexual/reproductive health and EPI. Some early demonstration projects were led by hospitals or non-governmental organisations (NGOs) with varying degrees of national immunisation team (EPI) involvement, a few operated without government input. Some interviewees from countries without a routine school/adolescent health programme reported confusion over which department should lead coordination of HPV vaccination and leadership was often decided opportunistically, based on who had capacity. However, it was clear that EPI involvement was necessary to ensure smooth implementation and reduce workload (e.g. to avoid establishment of parallel vaccine management and reporting systems). Delivery experiences with MOH ownership and high EPI involvement were more likely to achieve good coverage in comparison to others run by external partners or

with low EPI involvement. Sources indicated that to be effective, microplanning needed involvement of the Ministry of Education (MOE), teachers and school administrators and health representatives.

District selection

Among the 30 projects in 26 countries with data, areas included in half of the demonstration projects represented those with routine immunisation coverage and education performance similar to the national average (15 projects), a third represented convenient districts (i.e. close to the capital city and/or had good infrastructure; 10 projects), 47% were representative of both urban and rural areas (14 projects). Projects could be classified in more than one of these categories. Some projects selected districts that included varied or particularly challenging areas (23%, 7 projects) but 17% (5 projects) selected areas with higher than national average EPI coverage and educational attainment.

Enumeration of population eligible for vaccination

Accurate enumeration was challenging in most countries and affected estimations of the number of doses required, transport and coverage calculations. School headcounts/register checks used in conjunction with school enrolment rates, were the most accurate methods to calculate the target population number, aside from conducting a full census, which was prohibitively expensive in most countries. However, the number of out-of-school girls was often unknown throughout projects/programmes.

Cold-chain and waste management

The most efficient method of transporting HPV vaccines was alongside other routine vaccines. However, in some countries this proved problematic due to the demonstration project timeline not aligning with quarterly vaccine delivery schedules. Providing separate transport increased the cost of delivery. Routine national immunization cold-chain facilities were generally used. Waste management generally followed routine practices and needed improvement in many countries.

Staff training

Cascade training (i.e. national staff training regional staff, who train district-level, who train field-staff), was reportedly less expensive than transporting teams of national trainers around the country. However, periodic supervision was considered

necessary in order to ensure that the quality of information transfer between levels in the cascade was maintained.

Communications

HPV vaccination as a cancer prevention method was more frequently emphasized than its role in sexually transmitted infection (STI) prevention, in order to avoid stigmatising the vaccine and to reduce confusion with other STI prevention messages[14]. Messages targeted the whole community with information focused on cervical cancer, the importance of HPV vaccination, government endorsement, doses required, timing and venues, and lack of long-term adverse effects. Problems were reported when social mobilisation occurred less than a month before vaccination and high-level officials did not deal with rumours rapidly.

Delivery

Venue and target

Schools were the most commonly used vaccination venue, with 87% (58/67) of delivery strategies using them, with or without additional health facility or outreach components (Table 6.2). Strategies including schools gained high coverage but were reported to be resource intensive in countries without existing school-based health programmes. There were limited data on strategies that used health facilities as the only sites of vaccine delivery (6 experiences, 5 with coverage data). In experiences that used schools, 47% (26/58) vaccinated a specific age group of girls, 35% (19/58) selected a school grade(s) and 18% (10/58) vaccinated girls of a certain age within a specific school grade. Some MOH-led projects/programmes made changes to the delivery strategy for a variety of reasons that illustrate the trade-offs inherent in different strategies (Table 6.3).

Out-of-school girls

National primary school enrolment ratios indicate the proportion of girls out-of-school was 5% or less in 27% of the countries with data (9/34), between 6% and 20% in 62% of countries (21/34), and over 20% in four countries (range 23-37%)[15]. A third of experiences (33%) had no reported strategy for reaching out-of-school girls, another third (37%) relied on them attending health facilities for vaccination and the remaining experiences used outreach. Outreach was used in all four countries with poor school enrolment and reportedly increased coverage.

Duration of delivery per dose

Duration of delivery activities per dose ranged from 2-3 days to 20 days (data from 14 delivery experiences). Most experiences delivered each dose over the course of one week and activity was synchronized across districts (i.e. similar to a vaccination campaign). There was no obvious relationship between the duration of delivery activities per dose and vaccination coverage. However, countries reported that it was useful to provide a second opportunity for girls to obtain the vaccine (e.g. 'mop-up' vaccination days at schools) if they had initially refused or were absent.

Catch-up

Three national programmes conducted catch-up vaccination in older age groups (Bhutan, Rwanda, Vanuatu) either by vaccinating girls aged 9-15 or 9-18, or by additionally vaccinating the second and third grades of secondary school. No evaluation results were available for catch-up campaigns.

Health workforce

Almost all countries used qualified nurses to deliver the vaccine; one used community health workers (CHWs). CHWs and teachers were reportedly invaluable at vaccination venues to ensure efficient delivery. Disruption of other health services during HPV vaccine delivery was not homogenous within a country. Strategies to minimise the impact of the HPV school/outreach activities on routine services included: integration into existing outreach days, longer working days, use of staff from other areas or services and task-shifting responsibilities to CHWs. One country delivered each dose over a month instead of short 'campaign-style' delivery. Supervision was reported as necessary, but supervisor and vaccinator allowances and transport were frequently reported as being the drivers of high delivery costs.

Adverse events

Reported adverse events (AEs) were below 1% and minor across 45 delivery strategies in 34 countries that provided data. Monitoring, reporting and response procedures were consistent with those for other vaccines, although teachers were mentioned as a useful and, in some countries, novel resource in monitoring AEs.

Achievements: vaccine uptake, completion and coverage

Coverage was reported by 68% of experiences (49/72); only 10 projects conducted coverage surveys, the remainder relied on administrative coverage. Uptake, completion and final dose coverage achievements were high, with no estimates below 50% (Table 6.4). Factors correlated with high coverage in descriptive analyses were: including schools as a vaccination venue, high EPI and MOE involvement in both planning and implementation and including a strategy to reach out-of-school girls if school enrolment rates were variable. Other factors reported to encourage high coverage were: political commitment, good social mobilisation, community engagement and timely delivery of the vaccine on scheduled dates within one school year.

Integration

Projects implemented with MOH involvement generally used EPI structures and processes for vaccine delivery. However, the small scale of projects made integration difficult to assess and sometimes led to establishment of parallel processes for monitoring and evaluation, supervision, vaccine transport and staff remuneration, as HPV vaccine was not seen as part of the 'routine' workload.

Joint delivery of HPV vaccine with other interventions was limited. Seven projects/programmes attempted delivery with tetanus toxoid vaccine or deworming and vitamin A supplementation within school health programmes; five reported coverage estimates. There was no evidence that joint delivery affected HPV vaccine coverage when compared to strategies delivering HPV vaccine alone, although data were limited. Educational messages on reproductive health or hygiene issues were delivered at the same time as HPV vaccine in eight projects/programmes. Two externally-led projects/programmes delivered the first dose alongside a cervical cancer screening programme for mothers. No critical evaluations of joint delivery were available.

Financing and sustainability

Twenty-nine of the 55 demonstration projects were financed by GAP, through Axios Healthcare Development. GAP donated vaccine, but no delivery costs. Gavi funded nine demonstration projects and provided vaccine and some delivery costs. For the first year of implementation Gavi provided either US$ 4.80 per girl or US$50,000 for delivery, whichever amount was largest. In the second year, funding was halved to

account for start-up costs. PATH, through funding from the Bill and Melinda Gates Foundation and donated vaccine from GSK and Merck, financed four projects; 13 were supported by other means. Gavi, Merck, the Australian Cervical Cancer Foundation (ACCF) and national governments funded the national programmes.

Considerable uncertainty over the availability of future financing was reported by countries. The cost of school-based delivery was of concern for many where there were not existing school-based health programmes. In addition to the three delivery strategy changes in Table 6.3, four countries stated that they planned to change from a school-based strategy to a health facility-based strategy in the future, due to the high level of resources required for school visits, specifically for transport and staff per diems.

Discussion

There is now considerable experience in HPV vaccine delivery in LAMICs. School-based delivery to this target group is no longer 'novel'. Many lessons have been learnt that should make planning easier for countries still considering whether to introduce HPV vaccination. Recommendations (Table 6.5) and outputs for decision-makers are available online[16].

Our findings are limited by the variation in data availability; some topics were rarely reported, or the data were highly variable in quality (e.g. coverage). Representatives from eight countries did not respond or refused interviews particularly limiting data collection on scale-up experiences. As we relied on data supplied by country representatives, the availability of data may have been lower for less successful projects/programmes. Only nine Gavi-supported projects had completed their first year during the period of data collection.

Lessons learnt, drivers of high coverage and key messages were consistent across types of demonstration project and world regions, i.e. Africa (16 countries), Asia (10), Americas (6), Oceania (3), Europe (2). Lessons were similar to key findings documented during initial demonstration projects in 2007 [17, 18]. The dose schedule recommendation change in April 2014[19, 20] left insufficient time for much data on two-dose schedules to be included, but delivery will be logistically easier and less expensive than three doses. Limited EPI involvement is unlikely to be an issue in most future demonstration projects as involvement is required for Gavi

applications[9]. However, the substantial challenges in estimating target population size have not been stressed in previous publications[11, 17]. Enumeration accuracy impacted vaccine requirement projections and coverage calculations in almost all countries included. Teachers and health-workers should be trained in accurate enumeration and enforcing eligibility criteria.

Most experience to date is with school-based delivery. Funders should encourage countries to test different approaches; more data are needed on more sustainable strategies. If alternative strategies result in unacceptable levels of coverage, LAMIC may need increased funding to deliver school-based programmes. Limited attempts to reach out-of-school girls did not greatly affect coverage in countries that attain over 80% net school enrolment[15]. However, not providing an opportunity for out-of-school girls to be vaccinated perpetuates inequity.

HPV vaccine demonstration projects and national programmes to date in LAMICs have achieved high coverage. However, the expense of school-based delivery is of concern for the future sustainability of HPV vaccination programmes. Demonstration projects could better inform national programmes if they provided lessons in challenging areas and populations or tested more sustainable delivery strategies.

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Competing interests
None declared.

Author contributions
KG contributed to study design, protocol development, data collection and analysis, and drafted the manuscript. SMJ, NH and SK contributed to data collection and analysis. NH, SK, HB, and SMJ contributed to manuscript writing and interpretation.

DWJ, UG, MF, HB, and DSL contributed to study design and data interpretation and critically reviewed the manuscript. All authors read and approved the final version for submission.

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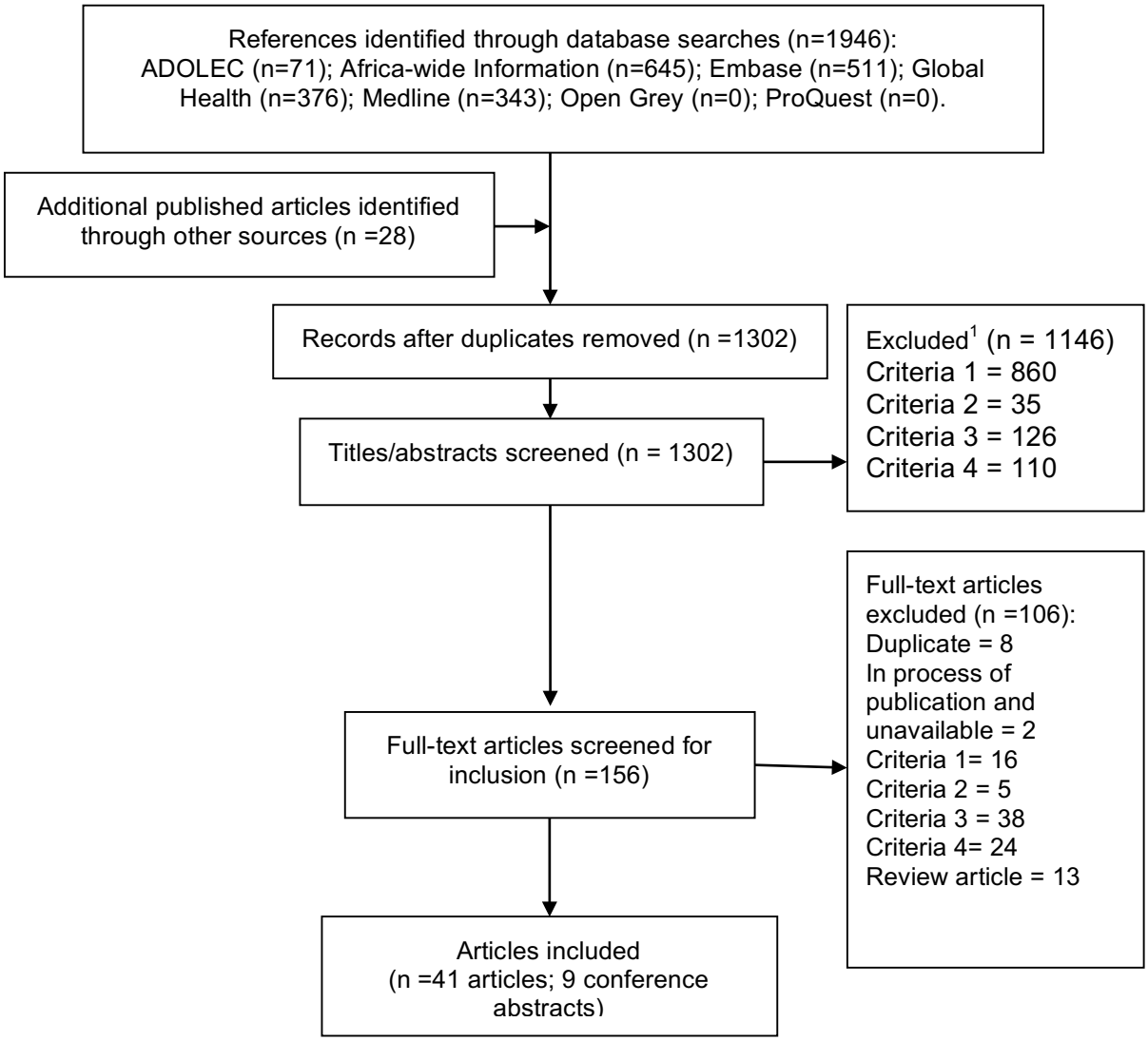
Figure 6.1 Systematic literature review flow



[1]Exclusion criteria for were: 1) not focused on HPV vaccination; 2) not focused on one of the 37 countries of interest; 3) did not include any results from after the vaccine was delivered; 4) not focused on, or relevant to, the demonstration project or vaccine introduction. Review articles were identified and searched for further references but were not included for data extraction.

Table 6.1 Key definitions

Delivery experience	The specific target population (age range in years or school grade) and vaccination venue (health facility-based, school-based, outreach, or a combination of the three) within a specific project/programme (defined by the funding source). E.g. A country that was funded for 2 years for a demonstration project and implemented one year of school-based delivery and a second year of health facility based strategy, was classified as having contributed information from one project but two delivery experiences.
Programme	A national HPV vaccination programme
Project	The activities funded through a specific GAP, Gavi or other funder support for a demonstration/pilot project. A distinct project was defined by the funder and/or implementer and grant award details.

Table 6.2 Countries included in this study and publications included from the systematic literature search of published literature.

Country	Income[1]	Primary school net enrolment ratio[2]	Demo[3]/ National (funding source)[3]	Vaccination venue(s)	Year/s HPV vaccination
Bhutan[1-3]	Lower-middle	88.1 (2013)	Demo (GAP)	School	2009
			National (ACCF)	School	2010
				Health facility + outreach	2011-13
				School + health facility + outreach	2014-
Bolivia[2,3]	Lower-middle	81.6 (2013)	Demo 1 (GAP)	School + health facility	2009
			Demo 2 (GAP)	School + health facility + outreach	2009
			Demo 3 (GAP)	School + health facility	2010
			Demo 4 (GAP)	School + health facility	2010-11
Botswana	Upper-middle	83.8 (2009)	Demo (WB)	School	2013
			Demo (MOH)	School + health facility	2014
			National (Govt.)	School + health facility	*2015*
Brazil[4-6]	Lower-middle	94.4 (2005)	Demo (GAP)	School	2010-11
			Demo (MOH)	School + outreach	2010-12
			National (Govt.)	School + health facility	2014-
Cambodia[2,3]	Low	98.4 (2012)	Demo 1 (GAP)	Health facility	2009-10
			Demo 2 (GAP)	School + health facility	2010-11
Cameroon[2,3,7-11]	Lower-middle	91.5 (2012)	Demo (GAP)	School + health facility	2010
Georgia[3]	Lower-middle	96.5 (2013)	Demo 1 (GAP)	Health facility	2010
			Demo 2 (GAP)	Health facility + outreach	2010-14
Ghana	Lower-middle	88.9 (2014)	Demo 1 (GAP)	School	2013
			Demo 2 (Gavi)	Year 1: School. Year 2: Health facility + outreach	2013-15
Guyana	Lower-middle	71.5 (2012)	Demo (GAP)	School + health facility	2012-13
			National (Govt)	NA	2014
Haiti[2,3]	Low	NA	Demo (GAP)	School	2009
Honduras[3]	Lower-middle	89.3 (2013)	Demo 1 (GAP)	School + health facility + outreach	2011
			Demo 2 (GAP)	School	2012-13
			Demo 3 (GAP)	School + health facility	2014
India[12-15]	Lower-	93.3 (2011)	Demo (PATH)	School + health	2009-10

Country	Income[1]	Primary school net enrolment ratio[2]	Demo[3]/ National (funding source)[3]	Vaccination venue(s)	Year/s HPV vaccination
	middle			facility campaign School and health facility monthly delivery	2009-10
Kenya[3,16]	Low	83.6 (2012)	Demo (GAP)	School	2011
			Demo (Gavi)	School	2013-15
Kiribati	Lower-middle	NA	Demo (GAP/ ACCF)	School	2011-13
Laos PDR	Lower-middle	97.3 (2013)	Demo (Gavi)	School + health facility + outreach	2013-15
Lesotho[2,3]	Lower-middle	79.6 (2013)	Demo 1 (GAP)	School	2009
			Demo 2 (GAP)	School	2010-11
			National	School	2012-
Madagascar	Low	77.1 (2003)	Demo (Gavi)	School + health facility	2013-15
Malawi	Low	96.9 (2009)	Demo (Gavi)	School + health facility	2013-15
Mali	Low	64.4 (2013)	Demo (GAP)	Health facility	2012
Moldova[3]	Lower-middle	87.9 (2013)	Demo (GAP)	School	2010-11
Mongolia	Lower-middle	94.7 (2013)	Demo (GAP)	School + health facility + outreach School	2012 2014
Mozambique	Low	87.4 (2013)	Demo (Gavi)	School + outreach	2014-15
Nepal[2,3,17]	Low	98.5 (2013)	Demo 1 (ACCF)	School	2008
			Demo 2 (GAP/ACCF)	School + health facility	2010
			Demo 3 (ACCF)	School + health facility	2011-14
Niger	Low	62.8 (2012)	Demo (Gavi)	School + outreach	2014-15
Papua New Guinea	Lower-middle	85.6 (2012)	Demo (GAP)	School + health facility	2012
Peru[13-15,18-23]	Upper-middle	91.8 (2013)	Demo (PATH)	School + health facility + outreach	2007-08 2009-10
			National (Govt)	School + health facility	2011-12 2014-
Philippines	Lower-middle	88.2 (2009)	Demo (Jhpiego)	NA	2010
Rwanda[24,25]	Low	93.4 (2013)	National (Merck)	School + health facility + outreach	2011-13
			National (Gavi)	School + health facility	2014-
Sierra Leone	Low	NA	Demo (Gavi)	NA	2013
South Africa[26-29]	Upper-middle	89.6 (2005)	Demo 1 (UCT)	Health facility	2010
			Demo 2 (KZN DoH)	School	2011
			Demo 3 (UoS)	School	2013
			National (Govt.)	School	2014-

Country	Income[1]	Primary school net enrolment ratio[2]	Demo[3]/ National (funding source)[3]	Vaccination venue(s)	Year/s HPV vaccination
Tanzania[3,15,30-35]	Low	83.5 (2013)	Demo (GAP)	School - age and grade criteria tested	2010-11 2010-11
			Demo (Gavi)	Year 1: School & health facility	2014- *2015*
Thailand[36,37]	Upper-middle	95.6 (2009)	Demo (Jhpiego)	NA	2010
Uganda[3,13-15,22,38-46]	Low	91.5 (2013)	Demo 1 (PATH/ MOH)	School + health facility	2008-09 2010-11
				School + health facility + outreach	2008-09 2010-11
			Demo 2 (GAP)	Health facility	2010
			Demo 3 (Merck)	School + outreach	2012-14
			Natl (Gavi)	*Health facility*	*2015-*
Uzbekistan[3]	Lower-middle	88.5 (2011)	Demo (GAP)	Health facility	2009
			National (Gavi)	*School + health facility*	*2016-*
Vanuatu	Lower-middle	98.9 (2005)	Demo (ACCF)	School	2009
			National (ACCF)	School + outreach	2013-
Vietnam[13-15,22,39,46-49]	Lower-middle	98.1 (2012)	Demo (PATH/ MOH)	School + health facility	2008-10
				Health facility	2008-10
Zambia	Lower-middle	91.4 (2013)	Demo (GAP)	School + health facility	2013-14

[1] World bank classifications of income group, February 2014.

[2] Information sourced from UNESCO Institute of Statistics, educational attainment most recently available data; year is indicated in brackets[50]

Italicised text indicates experiences with incomplete data due to start date, this data were obtained in the process of data collection when countries were questioned about future or current HPV vaccine activity; only experiences with at least one year of implementation were included in analyses.

Abbreviations: ACCF, Australian Cervical Cancer Foundation; CHW, community health worker; Demo, demonstration/pilot project; GAP, Gardasil® Access Program; est., estimated; HPV, human papillomavirus; KZN DoH, KwaZulu-Natal Department of Health; MOH, ministry of health; national, national programme; NA, not available; UCT, University of Cape Town; UNESCO, the United Nations Educational Scientific and Cultural Organisation; UoS, University of Stellenbosch; WB, World Bank.

Table 6.3 Changes in delivery strategy

Countries[1]	Original strategy	Change in strategy	Reasons for changes
Country 1	School	Health facility	High level of resources required for outreach visits to schools.
Country 1	Health facility	School	HPV vaccine coverage was low with health facility delivery.
Country 28	School + health facility + outreach	School + health facility	Outreach had proven resource intensive, with logistical difficulties and only incremental gains in coverage.
Countries 23, 8, 35	School	School + health facility +/- outreach	To increase equity of HPV vaccination by including out-of-school girls.
Country 7	Health facility	Health facility + outreach	To increase HPV vaccination coverage.
Countries 31, 33	School + health facility	Health facilities and integrated into routine outreach	High level of resources required for school-based strategy and concern over sustainability.
Countries	**Original target population**	**Change to target population**	**Reasons for changes**
Countries 1, 2, 24, 31, 33	Age	Grade	Identifying eligible girls by age was difficult if exact birth date/year was not known or documented. It was unacceptable to separate some girls from their classmates to receive the vaccine while other class members were not vaccinated (Country 24).
Country 31	Grade	Age	It is easier to explain to the community and aligns with routine EPI, which used age cohorts
Country 8	Grade	Age	To purposely assess a different strategy in the second year of the project.
Countries 8, 3, 33, 31	Grade	More appropriate grade	A higher concentration of eligible girls were in a higher/lower grade
Country 18	Age 10 out-of-school	Age 9-13 out-of-school	The relative ease of identifying 'pre-pubertal' girls around the age of 9-13 years in the community in comparison to trying to find exactly age 10 girls.

[1]Only countries where data are in the public domain are specifically named. Other countries have been allocated a number to anonymise them

Table 6.4 Coverage achievements across delivery experiences

Characteristic	Uptake (number (%))[1]				Completion (number (%))				Final dose coverage[2] (number (%))			
	≥90%	70-89%	50-69%	Total	≥90%	70-89%	50-69%	Total	≥90%	70-89%	50-69%	Total
School only	8 (57)	6 (43)	0	14	12 (67)	6 (33)	0	18	7 (39)	10 (56)	1 (6)	18
Health facility only	2(50)	2 (50)	0	4	1 (20)	4 (80)	0	5	2 (40)	1 (20)	2 (40)	5
School + health facility (+/- outreach)	15 (65)	8 (35)	0	23	15 (60)	10 (40)	0	25	14 (56)	6 (24)	5 (20)	25
All experiences	25 (60)	17 (40)	0	42	28 (58)	20 (42)	0	48	23 (47)	18 (23)	8 (17)	49

[1] Counts of the number of experiences achieving each category of coverage are presented with row percentages, i.e. among those strategies with data, 57% of school only strategies obtained ≥90% uptake compared to 50% of health facility strategies obtaining ≥90% uptake. Excludes projects/programmes that started in 2015 or later. Uptake is defined as the proportion of the target population that received the first dose of the vaccine schedule; Completion is the proportion of those who received the first dose of the vaccine who then also received the final dose of the vaccine schedule; final dose coverage is the proportion of the target population who received all recommended doses of the vaccine schedule.

[2]Coverage of a 2 or 3 dose regimen (only 2 experiences had coverage data on 2 dose regimen)

Table 6.5 Key Recommendations

Section	Recommendations
Preparation	- Planning processes should include representatives from the ministries of health, education and finance. - National immunisation programme involvement is critical for effective vaccine delivery.
Communications	- Social mobilisation in communities should begin early (at least one month before vaccination, earlier if possible). - Messages should focus on: cervical cancer prevention; safety and efficacy, including lack of fertility impact or long-term adverse effects, government endorsement, delivery timing and venues and the need to return for a second dose. - Members of government or WHO representatives should issue responses to rumours as quickly as possible.
Delivery	- In areas with variable school attendance, specific mobilisation of out-of-school girls and an opportunity for them to receive the vaccine should be provided. - If resources allow, planning a two-stage delivery of each dose can be successful in reaching those girls who initially refused vaccination. - Vaccination teams can include teachers and CHWs in order to decrease the number of qualified nurses needed for vaccine delivery sessions.
Achievements	- Including a component of school-based delivery can yield high coverage, if resources allow. If school enrolment is low, a mixture of strategies could be important in order to attain good coverage. - More evaluation of health facility only strategies is needed. - An opportunity for girls who missed doses to receive the vaccine should be supplied, either at return visits to schools or referral to health facility or outreach sites, depending on the resources available.
Sustainability	- More research should be conducted on scale-up experiences. - Further exploration of sustainable funding options should be conducted and disseminated, to encourage countries to scale-up demonstration projects.
Integration	- Rigorous evaluation of combined interventions with HPV vaccine delivery is needed to assess the effect on implementation, coverage, workload and cost. Funding agencies should systematically encourage this. - Gradual integration of processes into routine processes should be planned and formalised after the first round of vaccination is completed. - Opportunities to initiate or strengthen existing school health programmes and/or pre-adolescent/adolescent health should be seized through on-going collaboration with partners (e.g. MOE, reproductive health departments).

Supplementary Table 6.1 An example of the systematic search terms used and results retrieved in the database: Medline (OvidSP); 4th April 2016

Search		Results
1	Papillomavirus Vaccines/	5085
2	hpv.ab,ti.	26945
3	human papillomavirus.ab,ti.	23071
4	human papilloma virus.ab,ti.	3661
5	exp Immunization Programs/	10517
6	exp Vaccination/	70018
7	immuni$.ab,ti.	229073
8	vaccin$.ab,ti.	225394
9	2 or 3 or 4	33568
10	Immunization/	46296
11	5 or 6 or 7 or 8 or 10	415268
12	9 and 11	7745
13	1 or 12	8441
14	gambia/	2133
15	gambia.ab,ti.	1774
16	14 or 15	2621
17	limit 16 to yr="2014-Current"	150
18	13 and 17	0
19	senegal/	4852
20	senegal.ab,ti.	4103
21	19 or 20	6035
22	limit 21 to yr="2014-Current"	376
23	13 and 22	2
24	zimbabwe/	4890
25	zimbabwe.ab,ti.	3737
26	24 or 25	5778
27	limit 26 to yr="2014-Current"	299
28	13 and 27	0
29	chile/	10403
30	chile.ab,ti.	8360
31	29 or 30	12887
32	limit 31 to yr="2014-Current"	990
33	13 and 32	6
34	burkina faso/	2398
35	"burkina faso".ab,ti.	2409
36	34 or 35	2980
37	limit 36 to yr="2014-Current"	316
38	13 and 37	0
39	"cote d'ivoire".ab,ti.	1431
40	cote d'ivoire/	2595
41	39 or 40	2969
42	limit 41 to yr="2014-Current"	195

43	13 and 42	1
44	ethiopia/	7873
45	ethiopia.ab,ti.	6694
46	44 or 45	8911
47	limit 46 to yr="2014-Current"	1268
48	13 and 47	1
49	"solomon islands".ab,ti.	508
50	solomon islands/	892
51	49 or 50	1072
52	limit 51 to yr="2014-Current"	62
53	13 and 52	0
54	togo/	870
55	togo.ab,ti.	942
56	54 or 55	1134
57	limit 56 to yr="2014-Current"	89
58	13 and 57	0
59	bhutan/	240
60	bhutan.ab,ti.	288
61	59 or 60	361
62	limit 61 to yr="2009 -Current"	188
63	13 and 62	5
64	bolivia/	2013
65	bolivia.ab,ti.	2108
66	64 or 65	2792
67	limit 66 to yr="2009 -Current"	939
68	13 and 67	2
69	botswana/	1275
70	botswana.ab,ti.	1364
71	69 or 70	1648
72	limit 71 to yr="2013 -Current"	283
73	13 and 72	3
74	brazil/	62883
75	(brazil or brasil).ab,ti.	48616
76	74 or 75	75353
77	limit 76 to yr="2010 -Current"	29830
78	13 and 77	55
79	cambodia/	2388
80	(cambodia or cambodge).ab,ti.	2169
81	79 or 80	3029
82	limit 81 to yr="2009 -Current"	1277
83	13 and 82	5
84	(cameroon or cameroun).ab,ti.	4286
85	cameroon/	4051
86	84 or 85	5216
87	limit 86 to yr="2010 -Current"	1691

88	13 and 87	7
89	georgia/	9405
90	(georgia or Sakartvelo).ab,ti.	6753
91	89 or 90	12915
92	limit 91 to yr="2010 -Current"	2609
93	13 and 92	18
94	ghana/	5275
95	ghana.ab,ti.	5071
96	94 or 95	6357
97	limit 96 to yr="2013 -Current"	1228
98	13 and 97	1
99	guyana/	562
100	guyana.ab,ti.	623
101	99 or 100	897
102	limit 101 to yr="2012 -Current"	126
103	13 and 102	0
104	haiti/	2504
105	haiti.ab,ti.	1958
106	104 or 105	2948
107	limit 106 to yr="2009 -Current"	1325
108	13 and 107	9
109	honduras/	907
110	honduras.ab,ti.	1125
111	109 or 110	1361
112	limit 111 to yr="2011 -Current"	265
113	13 and 112	7
114	india/	82017
115	india.ab,ti.	53099
116	114 or 115	96520
117	limit 116 to yr="2009 -Current"	32162
118	13 and 117	100
119	kenya/	12121
120	kenya.ab,ti.	11071
121	119 or 120	14645
122	limit 121 to yr="2011 -Current"	3798
123	13 and 122	13
124	kiribati/	1003
125	kiribati.ab,ti.	110
126	124 or 125	1059
127	limit 126 to yr="2011 -Current"	163
128	13 and 127	0
129	(laos or lao).ab,ti.	2008
130	laos/	1391
131	129 or 130	2431
132	limit 131 to yr="2013 -Current"	404

133	13 and 132	0
134	lesotho/	311
135	lesotho.ab,ti.	422
136	134 or 135	481
137	limit 136 to yr="2009 -Current"	157
138	13 and 137	1
139	madagascar/	2581
140	madagascar.ab,ti.	3029
141	139 or 140	3543
142	limit 141 to yr="2013 -Current"	549
143	13 and 142	0
144	malawi/	3555
145	malawi.ab,ti.	3743
146	144 or 145	4441
147	limit 146 to yr="2013 -Current"	934
148	147 and 13	3
149	mali/	1862
150	mali.ab,ti.	2281
151	149 or 150	2754
152	limit 151 to yr="2012 -Current"	569
153	152 and 13	5
154	(moldova or moldavia).ab,ti.	516
155	moldova/	604
156	154 or 155	882
157	limit 156 to yr="2013 -Current"	98
158	157 and 13	2
159	mongolia/	1306
160	mongolia.ab,ti.	2126
161	159 or 160	2647
162	limit 161 to yr="2012 -Current"	747
163	162 and 13	1
164	morocco/	4302
165	morocco.ab,ti.	3413
166	164 or 165	5304
167	13 and 166	6
168	mozambique/	1622
169	mozambique.ab,ti.	1974
170	168 or 169	2323
171	limit 170 to yr="2014 -Current"	302
172	171 and 13	0
173	nepal/	5554
174	nepal.ab,ti.	5146
175	173 or 174	6611
176	limit 175 to yr="2008 -Current"	3107
177	176 and 13	6

178	niger/	947
179	niger.ab,ti.	8535
180	178 or 179	8706
181	limit 180 to yr="2014 -Current"	692
182	181 and 13	0
183	papua new guinea.ab,ti.	3512
184	papua new guinea/	2964
185	183 or 184	4294
186	limit 185 to yr="2012 -Current"	570
187	186 and 13	1
188	peru/	6144
189	peru.ab,ti.	6012
190	188 or 189	8298
191	limit 190 to yr="2007 -Current"	3606
192	191 and 13	26
193	(philippines or pilipinas or filipinas).ab,ti.	5438
194	philippines/	6935
195	193 or 194	8853
196	limit 195 to yr="2010 -Current"	1830
197	196 and 13	4
198	rwanda/	1649
199	rwanda.ab,ti.	1532
200	198 or 199	2072
201	limit 200 to yr="2011 -Current"	617
202	201 and 13	8
203	sierra leone.ab,ti.	1053
204	sierra leone/	948
205	203 or 204	1290
206	limit 205 to yr="2013 -Current"	377
207	206 and 13	0
208	south africa.ab,ti.	19388
209	south africa/	33165
210	208 or 209	37735
211	limit 210 to yr="2011 -Current"	8784
212	211 and 13	36
213	tanzania/	8464
214	tanzania.ab,ti.	7676
215	213 or 214	9927
216	limit 215 to yr="2010 -Current"	3322
217	216 and 13	17
218	thailand/	21183
219	thailand.ab,ti.	17744
220	218 or 219	26226
221	limit 220 to yr="2010 -Current"	7834
222	221 and 13	37

223	uganda/	8601
224	uganda.ab,ti.	8087
225	223 or 224	10265
226	limit 225 to yr="2008 -Current"	4692
227	226 and 13	32
228	uzbekistan/	1804
229	uzbekistan.ab,ti.	856
230	228 or 229	1999
231	limit 230 to yr="2009 -Current"	242
232	231 and 13	2
233	vietnam/	9403
234	vietnam.ab,ti.	8707
235	233 or 234	12413
236	limit 235 to yr="2008 -Current"	4654
237	236 and 13	27
238	zambia/	3347
239	zambia.ab,ti.	3148
240	238 or 239	4135
241	limit 240 to yr="2013 -Current"	640
242	241 and 13	3
243	18 or 23 or 28 or 33 or 38 or 43 or 48 or 53 or 58 or 63 or 68 or 73 or 78 or 83 or 88 or 93 or 98 or 103 or 108 or 113 or 118 or 123 or 128 or 133 or 138 or 143 or 148 or 153 or 158 or 163 or 167 or 172 or 177 or 182 or 187 or 192 or 197 or 202 or 207 or 212 or 217 or 222 or 227 or 232 or 237 or 242	398
244	developing countries/	65420
245	limit 244 to yr="2007 -Current"	17905
246	245 and 13	142
247	GAVI.ab,ti.	238
248	limit 247 to yr="2007 -Current"	213
249	248 and 13	31
250	(Low-income countries or LIC).ab,ti.	3274
251	limit 250 to yr="2007 -Current"	2510
252	251 and 13	19
253	(Low-middle income countries or LMIC).ab,ti.	456
254	limit 253 to yr="2007 -Current"	445
255	254 and 13	2
256	243 or 246 or 249 or 252 or 255	545

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6.4 Additional information

6.4.1 Data collection – Key informant interviews

The majority of interviews were conducted over the phone; however, 16 were completed in person through country visits or at international meetings. Interviewees underwent a formal informed consent process (Annex 6: Informed Consent Form) and interviews followed pre-defined topic guides (Annex 7).

6.4.2 Countries which have not initiated a demonstration project: sub-study

Stakeholders from nine Gavi-eligible countries that met the Gavi application criteria (national DTP3 coverage >70%) and that had a high burden of cervical cancer (>15/100,000 women/year), but had not yet applied to Gavi for HPV vaccination support, were approached for interviews (Table 6.6). Reasons for not applying and perceived barriers to implementation were discussed through telephone calls (Informed consent form Annex 6; Topic guide Annex 7). A further 11 countries that had not yet applied for Gavi support but either did not meet the eligibility criteria or had no cervical cancer data were not approached for interview (Table 6.7).

Among the nine countries that were eligible but exhibited no intention to apply for Gavi-support in 2015, we were able to interview five national immunisation programme managers. Four immunisation programme managers were unavailable or unresponsive to our approaches to participate by email and telephone. Acknowledging the importance of cervical cancer as a public health issue and awareness of Gavi funding for vaccine introduction, two countries were planning to apply to Gavi in the near future for HPV vaccine support. The remaining three KIs cited other competing priorities and insufficient capacity at the national coordination level together with inadequate political support and funding for the introduction as explanations for their lack of intention to apply for Gavi support for HPV vaccine. Interviews exposed the limited capacity at national level for multiple new vaccine introductions each year, especially given the administrative burden of funding applications and reporting requirements.

Table 6.6 GAVI-eligible countries that had not yet applied for HPV funding by January 2015 included in data collection (n=8)

Country*	World Bank classification of country economy[1]	DTP 3 coverage (2012 estimates unless otherwise stated)[2]	Incidence of cervical cancer (age-standardized rate per 100,000)[37]	Cervical cancer mortality rates (age-standardized rate per 100,000)[37]
Comoros	LIC	86%[3](WHO/UNICEF) 73% (HH survey)	61.3	40.3
Congo, DR	LIC	72%[3] (WHO/UNICEF) 89% (National) 62% (HH Survey 2010)	33.1	27.3
Djibouti	LMIC	81%[4](WHO/UNICEF) 81% (National) 61% (HH Survey 2006)	17.3	11.5
Eritrea	LIC	99%[3](WHO/UNICEF) 94% (National) 98% (HH Survey 2007)	17.4	13.1
Guinea-Bissau	LIC	80%[3](WHO/UNICEF) 90% (National) 81% (HH Survey 2010)	29.8	21.6
Kyrgyz Republic	LIC	96%[3](WHO/UNICEF) 96% (National) 85% (HH Survey)	23.7	11.2
Mauritania	LIC	80%[3](WHO/UNICEF) 80% (National) 57% (HH survey 2007)	29.4	18.8
Nicaragua	LMIC	98%[3](WHO/UNICEF) 108% (National) 95% (HH Survey 2006)	36.2	18.3
Nigeria[5]	LMIC	41%^(WHO/UNICEF) 57% (National) 38% (HH Survey 2013)	29.0	17.5

[1] LIC = low-income country; LMIC = lower-middle income country; UMIC = upper-middle income country

[2] Source: Gavi website; HH = Household

[3] No directly supporting data (low grade of confidence)

[4] Estimate supported by at least one data source either reported data, UNDP data or survey data.

[5] Nigeria was also included in data collection despite low DTP3 coverage due to a prior application and approval for a GAP project as the project was never started.

Table 6.7 GAVI-eligible countries that had not yet applied for HPV funding by January 2015 and considered ineligible for data collection.

Country	World Bank classification of country economy[1]	DTP3 coverage (2012 estimates unless otherwise stated)[2]	Incidence of cervical cancer (age-standardized rate per 100,000)[37]	Cervical cancer mortality rates (age-standardized rate per 100,000)[37]	Eligible for inclusion for data collection?
Afghanistan	LIC	71%[3] (WHO/UNICEF) 87% (National) 40% (HH Survey 2011)	8.8	6.9	No, incidence <15/100,000
Central African Republic	LIC	47%[3] (WHO/UNICEF) 59% (National) 32% (HH Survey 2010)	21.0	15.3	No, DPT coverage <70%
Chad	LIC	45%[3](WHO/UNICEF) 72% (National) 20% (HH Survey 2010)	18.8	14.6	No, DPT coverage<70%
Guinea	LIC	59%[3] (WHO/UNICEF) 102% (National) 50% (HH Survey)	38.4	27.9	No, DPT coverage <70%
Korea, DPR	LIC	96%[4](WHO/UNICEF) 96% (National) 92% (HH Survey 2008)	12.4	7.2	No, incidence <15/100,000
Pakistan	LMIC	81%[3](WHO/UNICEF) 89% (National) 65% (HH Survey 2013)	7.9	4.7	No, incidence <15/100,000
Somalia	LIC	42%[3] (WHO/UNICEF) 61% (National) 14% (HH Survey 2006)	33.4	20.1	No, DPT coverage <70%
South Sudan	LMIC	59% (WHO/UNICEF) 68% (National)	30.4	20.3	No, DPT coverage <70%
Sudan	LMIC	92%[4] (WHO/UNICEF) 92% (National) 59% (HH Survey 2010)	7.9	5.3	No, incidence <15/100,000
Tajikistan	LIC	94%[3] (WHO/UNICEF) 93% (HH Survey 2011)	9.9	4.9	No, incidence <15/100,000
Yemen	LMIC	82%[4](WHO/UNICEF) 82% (National) 61% (HH Survey 2006)	3.1	2.0	No, incidence <15/100,000

[1]LIC = low-income country; LMIC = lower-middle income country; UMIC = upper-middle income country
[2] Source: Gavi website
[3]No directly supporting data (low grade of confidence)
[4]Estimate supported by at least one data source either reported data, UNDP data or survey data,

6.4.3 Final country selection

A second phase of data collection was conducted after preparation of the results for the included manuscript (Section 6.4), extended data collection took place between November 2015 and May 2016. After this second phase the total number of countries included in the study increased form 37 to a total of 46 countries, 18 LIC, 22 LMIC, 5 UMIC and 1 HIC. The selection was representative of all low and lower-middle income countries (LIC and LMIC) that had at least 6 months experience of a demonstration project or national programme by 1st May 2016. In addition, 5 UMIC were included as they had experience of demonstration

projects and therefore potentially lessons around scale-up to national programmes. An innovative, unique dosing schedule using an interval of 12 months between campaigns to deliver the two doses in 1 HIC led to its inclusion in order to capture lessons that may be relevant to LIC and LMIC.

A further 6 countries were known to be planning or starting demonstration projects during the data collection period (Table 6.8). However, these countries had not completed 6 months of delivery by 1st May 2016 and were not included in data collection.

Table 6.8 Countries starting HPV demonstration projects in December 2015 or later (evaluation results were not available in time for this study)

	Country	Sponsor	Years of planned support[1]	Vaccine (preferred)
1	**Angola**	Donation	NA	NA
2	**Bangladesh**	Gavi	2015-16	Cervarix®
3	**Benin**	Gavi	2015-16	Cervarix®
4	**Burundi**	Gavi	Postponed	Cervarix®
5	**Liberia**	Gavi	Postponed	Gardasil®
6	**Sao Tome**	Gavi	2016	NA

'NA' indicates data not available. [1]Data collection ceased 1st May 2016

6.4.4 Project outputs

The third objective of the project was to disseminate key findings and recommendations in order to aid accelerated HPV vaccine introduction and scale-up. This objective was led by collaborators at PATH with key editorial input from the whole project team. The full set of outputs included an information pack of a 4-page overview and seven 2-page briefs (Figure 6.2), a slide deck, a video, an interactive world map and a poster. These are all freely available at www.rho.org/HPVlessons/ and have been widely disseminated during international workshops, meetings and conferences.

Figure 6.2 The 4-page overview and seven 2-page briefs, available in French and English

Figure 6.3 The 4-page overview and 2-page briefs in English

Lessons learnt

The review's findings confirm that **HPV vaccine delivery is feasible** in low- and middle-income countries and that countries worldwide have **the experience to demonstrate successful delivery.** Key findings and lessons include:

PREPARATION

- High-level political commitment led to more effective projects and national programmes.
- Collaboration between ministries of health and education increased project success.
- Delivery using routine vaccination programme models and resources created efficiencies.

COMMUNICATIONS

- Effective community mobilisation activities were conducted at least one month prior to vaccination, used multiple methods, and were carried out by health workers and community leaders.
- The most effective messages were: HPV vaccine prevents cervical cancer, is safe, will not harm future fertility, and is endorsed by the government and the World Health Organization.
- Face-to-face communication with parents and communities enhanced support and mitigated spread of rumours.
- Opt-out consent was more effective because opt-in consent generated refusals from parents and community suspicion.

DELIVERY

- Including schools in the delivery strategy attained the highest coverage.
- Enumerating the population before vaccination proved challenging but useful in developing vaccine registers.
- In schools, grade-based eligibility was logistically easier to implement than age-based eligibility.
- Delivery of all doses within one school year minimised drop-out and resulted in higher coverage.
- Use of community health workers assisted in identifying out-of-school girls and those who missed doses.
- Providing a second opportunity for vaccination was successful in reaching girls and parents who initially refused.

ACHIEVEMENTS

- All 49 projects/programmes with reported data achieved at least 50% coverage; and coverage for 41 of these was 70% or greater.

SUSTAINABILITY

- Recurrent financial delivery costs (excluding vaccines) were up to US$2.10 per dose. Annualised start-up costs represented up to 50% of all financial and economic costs.
- The cost of vaccines and delivery were critical for countries to estimate financial resources needed for sustainability.

Global project overview

More than 1,625,000 girls reached
(reports from 61 of 72 delivery experiences)

Estimated at least 837,800 girls fully vaccinated
(reports from 47 of 72 delivery experiences)

COMMUNICATIONS

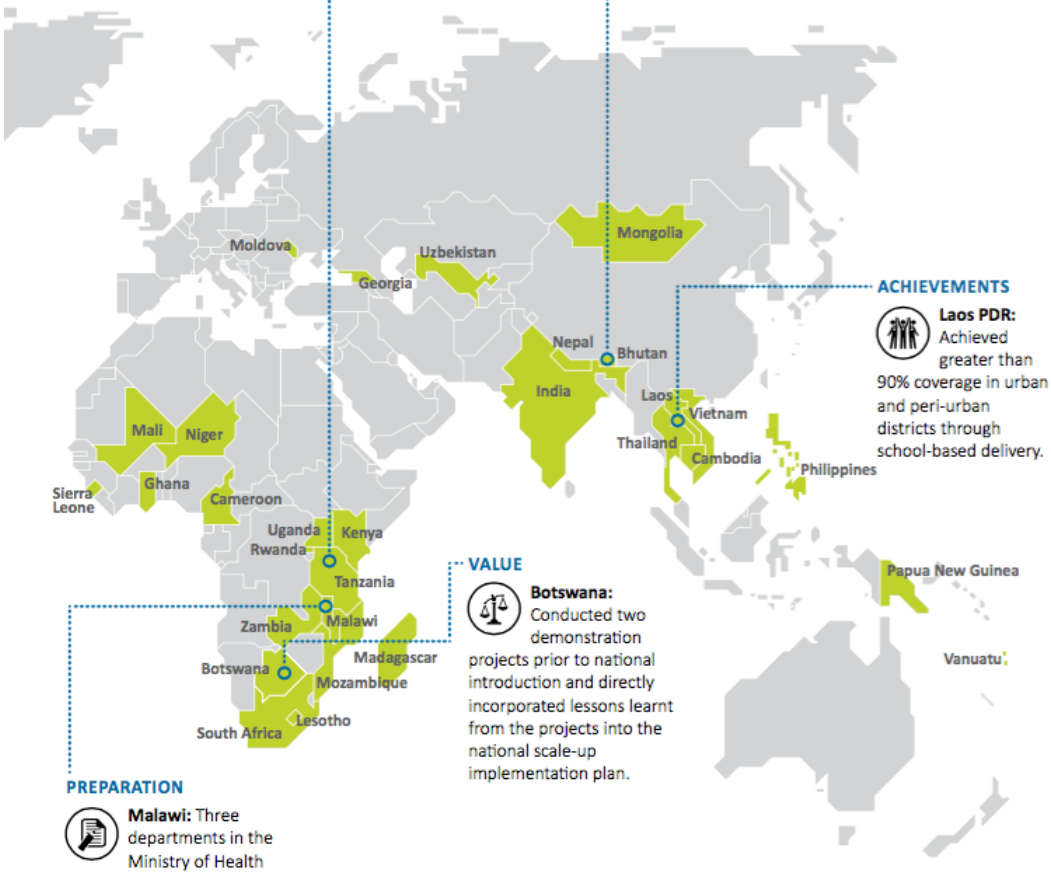
Bolivia: Carried out comprehensive community sensitisation using multiple modalities, including local media, well in advance of vaccination days.

DELIVERY

Tanzania: Successfully used schools for vaccine delivery and included opportunities for out-of-school girls to receive vaccine from their local health centre. Plans to test health centre-based delivery in 2015–2016.

SUSTAINABILITY

Bhutan: School-based and health facility-based delivery were implemented nationally in 2010 and 2011–2013, respectively. School-based delivery resulted in 20% higher coverage, so the country decided to use this approach from 2014 onward.



ACHIEVEMENTS

Laos PDR: Achieved greater than 90% coverage in urban and peri-urban districts through school-based delivery.

VALUE

Botswana: Conducted two demonstration projects prior to national introduction and directly incorporated lessons learnt from the projects into the national scale-up implementation plan.

PREPARATION

Malawi: Three departments in the Ministry of Health (Non-Communicable Diseases, Expanded Programme on Immunisation, Reproductive Health) worked collaboratively to plan and implement an HPV vaccine delivery programme with a high level of political commitment from the government.

PITFALLS

Lack of high-level political commitment for programme.

Lack of strong Expanded Programme on Immunisation involvement.

Poor coordination between health and school sectors for programmes using schools as a venue for delivery.

Difficulty in estimating target population at the district level from national and international data sources.

Underestimation of the power of negative media exposure.

Delays in distribution of funds for project and programme planning and implementation, and challenges with securing operational resources for ongoing vaccine delivery.

Non-engagement or delayed engagement with local community leaders in social mobilisation efforts.

Lack of engagement of private schools early in the planning process to ensure good collaboration.

Limited planning for vaccine delivery to hard-to-reach populations, such as girls not attending school.

BY THE NUMBERS

This brief summarizes a review of HPV vaccine delivery experiences comprising:

- **37** low- and middle-income countries
- **8** national introductions
- **55** demonstration projects or pilots
- **72** distinct experiences by countries
- **89** years of cumulative vaccination experience

KEY LESSONS

Preparation

Communications

Delivery

Achievements

Sustainability

Value

Pitfalls

The value and pitfalls of HPV vaccination demonstration projects

Countries that implemented demonstration projects reported on their value as well as potential pitfalls, including the following:

VALUE

- Projects provided valuable experience in planning and budgeting for school-based delivery, enumeration of girls, acceptable consent approaches, working with the ministry of education, and developing community education materials.
- Few countries took advantage of the opportunity in demonstration projects to test different combinations of venues, timing, eligibility, and co-delivery with other interventions.
- Selection process and small project size made some lessons learnt inapplicable to national rollout.

PITFALLS

- Poor coordination between the health and education sectors led to difficulties in engaging teachers and school delivery.
- Failure to correctly enumerate the target population in demonstration projects resulted in difficulties to accurately estimate coverage.

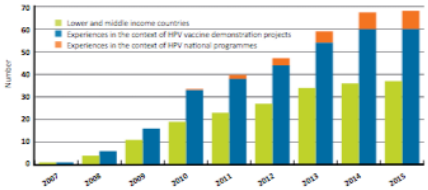
Countries now know what factors lead to successful HPV vaccine delivery, yet challenges remain to secure the political will and financial resources necessary to scale up and implement successful national programmes. This will take the **political and financial commitment of governments,** donors, and partners.

Project methodology

The project team conducted a cross-sectional retrospective review of country experience with delivery of HPV vaccines. The 37 countries selected for data analysis (see map) included those that had completed at least one year of a demonstration project or national programme by January 2015, low- or lower-middle-income countries that went straight to national introduction, and selected upper-middle-income countries that conducted a demonstration project (Figure 1).

Figure 1. Cumulative number of countries and experiences* with HPV vaccination

Low- and middle-income countries, January 2007–January 2015



*An HPV vaccine experience was defined by the specific target population and vaccination venue within a specific project/programme (defined by funding source). One country may have contributed multiple distinct experiences.

Data collection approaches included a systematic review of published literature, review of unpublished literature and project reports, and key informant interviews. In total, data were extracted from 41 published articles, 9 conference abstracts, and 124 unpublished papers and reports. To fill data gaps, the project team conducted key informant interviews with 27 project and programme implementers in 23 countries.

From February to May 2015, data were extracted using a standardised extraction matrix based on common elements to new vaccine introduction. Topics included national decision-making and planning, service delivery, health workforce, monitoring and evaluation, financial support and sustainability, and scale-up. These topics were further subdivided into 18 subcategories, with accompanying questions related to each.

Finally, the project team examined all qualitative data from the literature and interviews to produce aggregate topic summaries in cross-sectional thematic analyses. They analysed quantitative data (e.g., coverage and adverse events) descriptively to enable presentation of frequencies and proportions. Common reasons for acceptance and refusal were assessed across acceptability surveys using a scoring system. Data on social mobilisation activities were enumerated with coverage data and linked to acceptability data where possible.

This study was approved by the Ethics Committee of the London School of Hygiene & Tropical Medicine.

ACKNOWLEDGMENTS

The following entities are acknowledged for their contribution to this project and the delivery of HPV vaccines to more than one and a half million girls in low-resource countries:

- Governments, ministries of health, ministries of education, and national and other governmental departments.
- All programmes, nongovernmental organisations, and partners that implemented the HPV vaccine pilots, demonstration projects, and national introductions.
- All agencies that provided financial support and/or vaccine, in particular Axios International and Gavi, the Vaccine Alliance.
- All technical partners and international agencies that supported and advised countries on critical aspects of project planning, implementation, and evaluation.
- The Bill & Melinda Gates Foundation for financial support of this study.

The views expressed herein are solely those of the authors and do not necessarily reflect the views of PATH; the London School of Hygiene & Tropical Medicine; Axios International; Gavi, the Vaccine Alliance; or the Bill & Melinda Gates Foundation.

Photo: David Jacobs

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October 2015

PREPARATION

PATH

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

HPV Vaccine Lessons Learnt & Recommendations

Preparation

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of **HPV vaccination preparation.**

Findings and key lessons

DECISION-MAKING AND LEADERSHIP

In the review, the 26 countries with data about decision-making were largely motivated to implement HPV vaccine programmes based on high national cervical cancer burdens, availability of free vaccines, and financing support. Countries that secured political will during the preparation phases reported being able to gain interest and support at all levels. In most countries, the ministry of health was the lead institutional decision-maker, although leadership within the ministry of health varied by country and included a range of departments, including the national immunisation programme, noncommunicable diseases and reproductive health. The ministry of education was regularly cited as critical for success when schools were used as a delivery venue. For national programmes, a close relationship with the ministry of finance was identified as critical.

***Key lesson**: Timely intersectoral planning and coordination – across health and education sectors (and finance for national programmes) – was critical to successful implementation and sustainability.*

NATIONAL AND LOCAL PLANNING

Twenty-two of 33 countries described forming planning or interagency coordination committees at both national and subnational levels. Subnational committees were generally responsible for microplanning and requesting funds that were then forwarded to the national committee for approval and oversight. Countries reported that the most effective

PATH/Amyrah Jamohamed

microplanning efforts included involvement of various sectors, including teachers, school authorities and health representatives at the local level.

***Key lesson**: Cooperation between local representatives from the health and education sectors facilitated effective microplanning.*

INTEGRATION WITH NATIONAL IMMUNISATION PROGRAMMES

HPV vaccination was frequently delivered through the national immunisation programme and shared the same structures and resources, including staff and logistical capacity. Processes were also similar across microplanning, communication, social mobilisation, training and logistics. A number of projects/programmes indicated that planning, social mobilisation and supervision processes for the newly introduced HPV vaccine required more intense resource mobilisation and preparation.

***Key lesson**: Where the national immunisation programme led HPV vaccine demonstration projects, integration with routine activities was generally strong, and existing human resources and infrastructure were used to deliver the HPV vaccine.*

STAFF CAPACITY, TRAINING, REMUNERATION AND WORKLOAD

Health care workers who delivered routine vaccinations were also responsible for HPV vaccination. Among 22 delivery experiences with human resource data, the most common vaccination team size was three to four persons, comprising two health workers, one mobiliser and one teacher.

Among the 15 countries with information on staff training, 13 used a 'cascade' training and supervision model. Initial training was provided to the national immunisation team. National team members then trained district representatives, who subsequently trained frontline staff. Eight countries used a supervisory approach in which national-level staff supervised staff at the provincial/district levels and district staff supervised health workers. Training duration varied from less than a day to three days.

The impact on staff workload varied depending on delivery strategy and planning approaches. Among ten countries with data on the impact of HPV vaccine activity on routine health service provision, six countries reported no impact, while four reported that other routine services were affected temporarily. Importantly, five of the countries reporting no impact put mitigation strategies in place, such as additional temporary staff, prior to delivery.

All 17 projects/programmes with remuneration data used allowances to pay health workers for outreach or other activities outside the health facility, typically at standard government rates. This strategy posed a challenge in demonstration projects that were not integrated with routine activities. Several countries indicated that making HPV vaccination part of routine activities might reduce allowance payments.

Key lesson: *The 'cascade' approach was the most common method of training and supervising staff. Carefully monitoring training and strengthening the capacity of supervisors proved critical to preparing vaccination teams.*

Key lesson: *Staff and supervisor allowances and transport to schools tended to be expensive; these costs were considered a key consideration for ongoing sustainability.*

VACCINE TRANSPORT

Two national programmes and 22 of the 29 demonstration projects with data on transportation used national immunisation programme systems to transport HPV vaccine. In some projects, assumptions that HPV vaccine would be transported with other vaccines proved problematic when the demonstration project did not align with quarterly vaccine delivery schedules and separate transport for HPV vaccines had to be arranged.

Key lesson: *Coordinating transportation of HPV vaccines with routine vaccines reduced logistical challenges and costs.*

Recommendations

Based on country experience, decision-makers preparing for future HPV vaccine programmes should:

1. **Ensure that the national-level planning process includes leadership and endorsement from the ministry of health, ministry of education and – particularly for national programmes – the ministry of finance.** Allow at least nine months in most cases for decision-making and planning at national and subnational levels.
2. **Make certain that the national immunisation programme feels ownership of HPV vaccination and is actively involved in each phase.** This support and participation in planning and implementation are critical for effective delivery.
3. **Conduct a human resources capacity assessment to determine vaccination team size.** Team size will depend on the number and size of schools in the catchment area and organisation of other outreach activities.
4. **Ensure adequate supervision when adding HPV vaccination to health workers' workload.** Integrating HPV supervision with other routine oversight can decrease costs.
5. **Carefully consider whether and how to allocate allowances during planning.** Integrating HPV activities with other outreach and school health programmes so that allowances are shared can help to minimize costs.
6. **Plan HPV vaccine transportation closely and well in advance with the broader national immunisation system.** Transporting HPV vaccine with other routine vaccines maximizes cost efficiencies.
7. **Conduct training at least two months before delivery and include all involved teachers and health workers, not only those delivering the HPV vaccine.** Allowing adequate time between training and delivery improves community response to credible influencers.

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent 8 national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

Additional topic summaries address communications, delivery, achievements, sustainability, value and pitfalls. Find those briefs and more information at www.rho.org/HPVlessons.

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ACHIEVEMENTS

HPV Vaccine Lessons Learnt & Recommendations

Achievements

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of **HPV vaccination achievements.**

Findings and key lessons

VACCINE COVERAGE

Forty-nine of a total of 72 HPV vaccine delivery experiences had data on final dose coverage. Coverage was defined as the total number of girls receiving all HPV doses out of the total estimated eligible population. In general, coverage was good, with 84% of delivery experiences reporting 70% coverage or higher. No project/programme reported less than 50% coverage. Of those reporting coverage, 47 used a three-dose schedule and 2 used a two-dose schedule (revised recommendations from the World Health Organization for the two-dose schedule were only released in late 2014).

Only five projects/programmes that vaccinated solely in health facilities reported coverage; in general, these had lower coverage than those that included schools. One national programme that employed different strategies over a five-year period found that school-based delivery resulted in 90% coverage, compared to 65% coverage using health-facility-based delivery.

***Key lesson**: Achieving high HPV vaccine coverage is feasible in low- and middle-income countries.*

***Key lesson**: Vaccine delivery strategies that included a school-based component resulted in higher coverage, compared with those that only used health facilities for vaccinations.*

UPTAKE AND DROPOUT

Vaccine uptake (first-dose coverage) reported by 28 delivery experiences ranged from 74% to greater than 100%. Completion rates (proportion of initiators receiving all doses) were reported by 48 delivery experiences and ranged from 73% to 99%. Sixty per cent of reported delivery experiences achieved a vaccination completion rate of 90% or more.

PATH/Scott LaMontagne

Several factors helped with tracking doses, including vaccination registers (electronic or manual), immunisation cards, school staff involvement and reminders through health workers, churches and community forums.

***Key lesson**: Vaccination registers, immunisation cards and utilisation of community members facilitated tracking girls to ensure completion of all vaccine doses.*

FACTORS ASSOCIATED WITH HIGH COVERAGE

Data from 49 delivery experiences showed that factors correlated with high coverage (≥70%) included using schools as a location for vaccinations, leadership by the Expanded Programme on Immunization, planning and implementing in collaboration with education ministries and departments at national and subnational levels, and including vaccination opportunities for out-of-school and absentee girls. Other factors included comprehensive social mobilisation that deployed 'credible influencers', such as health workers and teachers, and vaccination registers and cards. Vaccination by grade was reported to be logistically easier to implement than vaccination by age, when using schools.

PATH/Le Thi Nga

Key lesson: *Strategies that included a school-based delivery component were most likely to achieve high coverage due to the ability to reach a large number of eligible girls at the same time and place. (There was little experience of health-facility-only delivery strategies.)*

Key lesson: *Involving the national immunisation programme and education sector at national and local levels during planning and implementation was critical for high coverage.*

Key lesson: *Other factors associated with high coverage included using vaccination registers and cards and social mobilisation that deployed credible influencers.*

FACTORS ASSOCIATED WITH LOW COVERAGE

Among 49 delivery experiences, lower coverage was observed in some of those using only health facilities, those that did not effectively coordinate and plan vaccinations with schools, and where rumours led schools to refuse vaccination. Several delivery strategies with low coverage also noted delays in receiving funds for social mobilisation activities and vaccinations. Not providing a second opportunity for girls who missed the first dose was also noted as a factor correlated with decreased coverage.

Key lesson: *Lack of effective planning and coordination with schools negatively impacted coverage.*

VACCINE COVERAGE DATA COLLECTION AND REPORTING

Coverage data accuracy was variable, and only 28 of 49 delivery experiences described how they recorded and reported data. Some reported the number of girls vaccinated out of the target population, while others only reported a percentage. Estimates of the target population were variable and influenced by a wide range of data sources. How well health workers, teachers and parents understood vaccination eligibility criteria also influenced the quality and accuracy of coverage data.

Recommendations

Based on country experience, decision-makers wanting to increase coverage for future HPV vaccination programmes should:

1. **Conduct joint planning with the national immunisation programme and education sector at national and local levels well in advance of vaccine launch.** This will ensure well-coordinated activities and more accurate data on the target population.
2. **Distribute funds early for planning, mobilisation and implementation activities.** Delays negatively affect coverage.
3. **Use schools as vaccination sites to maximise coverage.** Ensure that vaccination opportunities are in place to reach absentee and out-of-school girls.
4. **For efficient delivery, use grade-based eligibility criteria in schools where age-based selection is difficult.** However, continue to collect age data for reporting requirements.
5. **Engage teachers, community health workers and the wider community to identify out-of-school or absentee girls and track girls between doses.** Community involvement increases uptake and completion of all doses.
6. **Carefully monitor and evaluate coverage.** These are important in order to understand whether approaches are effective or changes are needed during the project/programme.

Ten delivery experiences in six countries reported coverage data from population-based surveys. These were considered to be more accurate and reliable measures of HPV vaccine coverage, and were used to validate estimates from administrative data.

Data collection was reported to be challenging due to the unique target population, the need to track multiple doses for each girl, a lack of standardized forms and harmonization with routine vaccination forms, and difficulties in accurately recording age. Variable requirements by donors for grade-specific and age-specific coverage data also presented challenges.

Key lesson: *Data collection and achieving data accuracy posed challenges for most countries, based on a range of factors specific to HPV vaccination.*

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent 8 national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

Additional topic summaries address preparation, delivery, communications, sustainability, value and pitfalls. Find those briefs and more information at www.rho.org/HPVlessons.

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COMMUNICATIONS

HPV Vaccine Lessons Learnt & Recommendations

Communications

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of **HPV vaccine communications.**

Findings and key lessons

FORMATIVE RESEARCH AND MESSAGES

Only seven countries in the review indicated that they had conducted formative research to inform communications activities. They found that knowledge of cervical cancer, HPV and HPV vaccination was low in communities, including among teachers and health workers.

PATH/Minh Lam-Bamed

When developing messaging, most projects/programmes framed vaccination as preventing cancer rather than preventing a sexually transmitted infection. This was because audiences related better to cervical cancer prevention. Furthermore, health decision-makers were concerned that associating HPV vaccination with sexually transmitted infections might increase stigma and decrease parental acceptance. Secondary messages focused on vaccine safety and efficacy, where and how it would be delivered, whether consent was necessary, and countering misinformation or specific rumours.

Several countries reported rumours. The range of rumours was limited and the content was consistent: fear that HPV vaccination might reduce fertility or cause adverse events. Strategies to address rumours included tailoring of messages to counter specific fears, vaccine endorsements by high-level officials, and dissemination of letters detailing World Health Organization or government endorsement of the vaccine's safety.

Key lesson: *Most countries used the following messages to encourage parental and community acceptance: HPV vaccine prevents cervical cancer, is safe, will not harm future fertility, and is endorsed by the government and the World Health Organization.*

MATERIALS AND TACTICS

Countries employed multiple communication channels to deliver messages. Interactive methods included individual or group meetings at schools and health facilities with teachers and health workers. Non-interactive methods included leaflets, posters, community announcements, radio and television.

Communication was reported to be most effective when delivered by 'credible influencers', such as health workers, teachers and community or religious leaders. Most parents reported that they first learned about the vaccine from meetings and other communication with health workers or teachers. They also reported a preference for interactive information sources.

Key lesson: *Face-to-face interaction was the most effective way of mobilising parents and communities, especially with groups that were likely to refuse vaccination or that were exposed to antivaccination rumours.*

Key lesson: *The most effective influencers were health workers, teachers and community leaders.*

SOCIAL MOBILISATION TIMING AND SEQUENCING

Most countries that reported data began mobilisation activities at least a month before vaccination; the success was greatest

when activities were coordinated with health, education and community leaders. Implementation activities included health worker and teacher training, and meetings with parents or students. These activities were conducted by nurses, school leaders or teachers. A few demonstration projects used house-to-house visits, which were well received. While the timing of social mobilisation activities did not seem to affect coverage, projects/programmes reporting delays in social mobilisation indicated that implementation was difficult.

Key lesson: *Community sensitisation and mobilisation activities that were conducted at least one month prior to vaccination were most effective.*

ACCEPTABILITY

Among eight countries that conducted postvaccination acceptability surveys of parents or caregivers, the most common reasons parents agreed to vaccination were to protect their children from cancer, because vaccines are good for health and because they perceived their daughters to be at risk of cervical cancer.

Information related to acceptance and refusal of HPV vaccine was obtained from 32 delivery experiences in 23 countries. Those most likely to refuse vaccination were parents (in seven projects/programmes), private schools (in five projects/programmes) and religious or antivaccine groups (in five projects/programmes). Some projects/programmes noted that with persistent sensitisation through community influencers, vaccine acceptability increased in communities that were initially reluctant.

Seven countries provided data from surveys on why HPV vaccination was not started or completed. The three most common reasons cited by parents for not starting vaccination were fear of adverse effects, lack of awareness of the project/programme, and absenteeism during school vaccination days. Once started, the main reasons for noncompletion were logistical.

Key lesson: *Logistical challenges, such as lack of awareness of vaccination days and school absenteeism, were common reasons for nonvaccination and incomplete vaccination.*

Key lesson: *Vaccine safety concerns, rumours and attending a private school were associated with nonvaccination.*

CONSENT

Fifty out of 72 delivery experiences had data on the parental consent method for HPV vaccine. Consent policies were largely aligned with country-specific national policy. 'Opt-in' consent (where parents must agree to vaccination) was used in 58% of experiences, while 30% used 'opt-out' consent (where vaccination proceeds unless parents indicate otherwise).

Six countries reported that using an opt-in policy, when opt-out policies were used for other vaccinations, led to suspicions that HPV vaccine was more risky than routine vaccines. Seven other countries changed to an opt-out strategy after one year of implementation. Experiences showed that a lengthy or complex consent process resulted in some girls missing the opportunity to be vaccinated.

Key lesson: *Opt-in consent, where not used for routine vaccines, increased rumours that the vaccine was experimental and unsafe. An opt-out approach appeared acceptable where implemented.*

Key lesson: *Lengthy consent procedures decreased consent/uptake, as parents found it logistically difficult.*

Recommendations

Based on country experience, decision-makers conducting communications for future HPV vaccine programmes should:

1. **Develop a communication plan to inform social mobilisation activities.** This should include strategies to prevent and manage rumours, measures to adequately mobilise private schools, and a plan for delivering messages to out-of-school and hard-to-reach girls.
2. **Engage early with community groups, including schools and churches.** In-person meetings are the most effective method for increasing acceptance and confidence in vaccination.
3. **Focus messages on cervical cancer prevention, vaccine safety and efficacy, government endorsement, and when and where to get vaccinated.** Train teachers, community leaders and health workers to deliver messages, and adequately respond to questions and concerns from parents and the community.
4. **Tackle emerging rumours as soon as possible.** To do so, use respected institutions and high-level officials.
5. **Begin social mobilisation at least one month before vaccination.** In addition, ensure adequate and timely funding and preparation time to develop social mobilisation materials.
6. **Ensure consistency with existing consent policy.** Where possible, use 'opt-out' processes.

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent 8 national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

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DELIVERY

HPV Vaccine Lessons Learnt & Recommendations

Delivery

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of **HPV vaccine delivery.**

PATH/Jacqueline Sterns

Findings and key lessons

DELIVERY STRATEGY

Most projects/programmes implemented a delivery strategy that used schools as the venues for vaccination, either alone or in combination with health facilities, and with or without outreach for out-of-school and absentee girls. Health workers who visited schools worked closely with teachers. Strategies that incorporated schools were reported as resource intensive; however, these strategies also achieved the highest coverage. Countries that used community health workers for vaccine delivery cited positive outcomes, such as reduced workload for health workers and better access to hard-to-reach areas and groups.

Key lesson: *Delivery strategies that used schools reached large proportions of 9- to 13-year-old girls and benefited from coordination with teachers. However, these strategies were resource intensive.*

Key lesson: *Engaging community health workers increased community acceptance and coverage, and assisted in identifying girls who were out of school or who missed doses.*

DISTRICT SELECTION AND DEFINITION AND ENUMERATION OF TARGET POPULATIONS

For 30 demonstration projects across 26 countries, district selection was based on the following criteria: average conditions that represent a 'typical' district, convenience and practicality, a range of conditions to allow comparison (e.g. urban, rural, hard-to-reach), or particular challenges that required additional testing and practice.

To define the population, 47% of the delivery experiences that used schools targeted a selected age group of girls, 35% selected school grade(s) and 18% identified a selected age group within a selected grade. All projects/programmes that employed only health-facility and/or community-outreach delivery strategies identified girls by age.

Across 32 demonstration projects and five national programmes, the most common methods used to estimate the number of girls targeted were school registers, enrolment data from the ministry of education, or the most recent census data combined with survey estimates on school attendance. In almost all cases, none of these sources provided reliable denominators for planning vaccination and estimating vaccine coverage. In most countries, a headcount of eligible girls was taken a few weeks before vaccination and during the first-dose delivery, which allowed numbers to be adjusted prior to delivery of the next dose(s).

Key lesson: *A grade-based delivery strategy was simpler to implement in schools, although it was challenging to communicate why same-age girls in different grades would not be vaccinated. An age-based strategy was easier to explain to the community and aligns with the routine vaccination programme but could cause greater disruption in schools by vaccinating girls across multiple grades.*

PATH/Le Thi Nga

Key lesson: *Across nearly all countries, estimating the target population for demonstration projects posed a considerable challenge.*

Key lesson: *Microplanning can include an exercise to enumerate all schools – including those not registered with the ministry of education – and establish reliable registers to be validated during first-dose delivery.*

DURATION

HPV vaccine was delivered through a campaign-style approach in almost all projects/programmes, with the time allowed for delivery of each dose ranging from two days to two weeks. One week was the most common duration.

Among 16 countries, common strategies for following up girls who missed doses included directing girls to health facilities, returning to schools for a second vaccination session, or administering the missing dose at the next scheduled dose (i.e. starting dose one at the time of dose-two delivery).

Key lesson: *The scope of follow-up activities for girls who did not receive the first dose was generally governed by country-specific factors such as school absenteeism, perceived 'adequate' coverage and available resources.*

Key lesson: *Delivery of all doses within one school year minimised dropouts and facilitated tracking girls to complete all doses.*

Key lesson: *Where resources allowed, providing a second opportunity for vaccination was successful in reaching girls and parents who initially refused.*

ADVERSE EVENTS FOLLOWING IMMUNIZATION AND SAFE INJECTION PROCEDURES

In most countries, adverse events following immunization (AEFIs) were reported on standardised forms at vaccination sites. Reported AEFIs were below 1% among 34 countries with any data. Most AEFIs were minor and temporary, requiring observation but no or minimal treatment.

Most countries indicated availability of injection safety guidelines and/or training procedures. Where these were lacking, countries suggested that they 'generally adhered' to safe practices.

Key lesson: *Adverse event training, monitoring and response procedures were generally considered acceptable and consistent with those of other vaccines; some projects/programmes monitored adverse events more closely for HPV vaccines.*

Recommendations

Based on country experience, to devise a successful delivery strategy for future HPV vaccine programmes, decision-makers should:

1. **Target schools as the most efficient way to reach most 9- to 13-year olds.** However, where school enrolment is low, a combination of delivery strategies is essential to achieve high coverage.
2. **Consider a range of factors when selecting a delivery strategy.** These should include the proportion of the target group in school, absenteeism rates, operational costs, desired/adequate coverage, and human and financial resources required for programme sustainability.
3. **Implement a specific mobilisation strategy for out-of-school girls.** This might include messages about the nearest health facility where the vaccine can be accessed or other targeted vaccination opportunities.
4. **Assess the cost-effectiveness of follow-up activities, such as return visits to schools with low coverage rates.** Having a coverage threshold may be a way to identify areas where these activities will likely yield the most benefit.
5. **Establish a robust records system during implementation of the first dose.** This will be important for future target group calculations and for tracking subsequent doses.
6. **Have standardised national guidelines and training procedures for reporting and responding to adverse events.** Stakeholders who are not part of the national immunisation programme, such as teachers and parents, can be a useful resource in monitoring and reporting adverse events.

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent eight national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

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SUSTAINABILITY

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HPV Vaccine Lessons Learnt & Recommendations

Sustainability

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of **HPV vaccine sustainability.**

Findings and key lessons

FINANCING AND COSTS

Across the review, 55 demonstration projects in 36 countries received support through vaccine donations and/or contributions towards delivery costs. This support was provided by various partners, including the GARDASIL® Access Program through Axios International; Gavi, the Vaccine Alliance; Merck & Co., Inc. and the Bill & Melinda Gates Foundation through PATH; the Australian Cervical Cancer Foundation; the Cancer Institute Foundation through Jhpiego, an affiliate of Johns Hopkins University; and country-based funders.

In 11 countries with national programmes, Merck & Co., Inc.; Gavi; the Australian Cervical Cancer Foundation; and national governments (in middle-income countries) provided financing.

Four countries provided detailed, published estimates on both the financial and economic costs of HPV vaccine delivery, excluding vaccine costs. Financial costs - expenditures for planning and implementation - ranged from US$1.11 to $2.10 per dose. Economic costs - including opportunity costs such as staff time - ranged from $1.44 to $3.88 per dose. Annualised start-up costs represented up to 50% of all financial and economic costs. Delayed disbursement of implementation funds, particularly for transportation and health-worker allowances, also affected key activities, such as social mobilisation and the provision of transport for health workers.

Key lesson: *Despite vaccine donation, the financial cost of vaccine delivery (up to $2.10 per dose) was perceived to be high by project/programme implementers.*

Key lesson: *Funding provided for implementation typically covered a share of delivery costs, although some countries reported this was inadequate.*

Key lesson: *Start-up costs represented up to 50% of financial and economic costs and were particularly challenging to finance; underestimating them led to disruption of activities.*

Key lesson: *Transportation costs and allowances for health workers and supervisors were key drivers of delivery costs.*

PATH/Scott Lalvontagne

FACTORS INFLUENCING SCALE-UP

Important lessons about cost drivers influenced countries' perspectives on scale-up. Out of 21 countries with information about scale-up that had not yet started a national programme, only 3 expressed relative certainty about future financing and ongoing political commitment for HPV vaccination. Seven reported that they were not planning to scale up in the foreseeable future, and the remaining countries expressed considerable uncertainty about financing of national introduction.

For several countries, the fact that they were not, or no longer, eligible for Gavi support was a major barrier to scale-up. A few

PATH/Robin Bielik

countries intended to implement a direct agreement with Merck & Co., Inc., while others indicated they would continue with another demonstration project if funds were available.

Several countries noted that experience gained from demonstration projects had provided important insights about the financial and operational planning needed to garner the resources necessary for national introduction.

Key lesson: *Because start-up and delivery costs were found to be high, countries expressed concern about securing the financial resources necessary for national scale-up.*

Key lesson: *Vaccine costs were considered a significant issue for sustainability, especially in countries that were not eligible – or were soon to graduate from eligibility – for Gavi support.*

Key lesson: *Estimates of delivery costs were important to inform country planning on securing adequate financial resources for national introduction.*

Recommendations

Based on country experience, decision-makers assessing financing of HPV vaccination in view of national scale-up should:

1. **When implementing a demonstration project, test different delivery strategies, compare implementation costs and identify a sustainable option.** Strategic design and implementation can help identify efficiencies, areas for cost savings and the best delivery options.
2. **Share operational costs with the national immunisation programme to reduce costs of implementation.** This might include costs for allowances or transportation.
3. **Explore sustainable funding options and expand the funding base beyond Gavi.** Countries no longer qualifying for Gavi support should note that vaccines are offered at the Gavi-purchased price following the countries' graduation from eligibility for Gavi support.
4. **Call for and facilitate additional research on scale-up experiences.** In particular, countries would profit from further research on the costs of a variety of HPV vaccine delivery approaches at national scale.

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent 8 national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

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VALUE

HPV Vaccine Lessons Learnt & Recommendations

Value

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations relevant to the theme of the **value of HPV vaccine demonstration projects.**

Findings and key lessons

BACKGROUND ON HPV VACCINE DEMONSTRATION PROJECTS

Prior to 2012, access to HPV vaccine for many low- and middle-income countries was limited to demonstration projects, through vaccine donations to the government, or via an external partner. Because of the high cost of the vaccine, national rollout was not an option for the vast majority of countries. In late 2012, access to HPV vaccine was made more widely available to low-income countries through support from Gavi, the Vaccine Alliance. The purpose of these demonstration projects was for countries to test the delivery of this new vaccine, which targeted a novel population (young adolescent girls), and to pave the way for countries to build the capacity and infrastructure needed to vaccinate girls nationwide.

This review focused on 37 low- and middle-income countries that conducted HPV vaccination demonstration projects or national programmes. Their cumulative experience is important for countries that are considering how to introduce HPV vaccination.

EXPERIENCE GAINED THROUGH DEMONSTRATION PROJECTS

While 36 countries in the review had a range of experiences with implementing demonstration projects, in general they benefited from 'learning by doing'. Demonstration projects allowed countries to gain knowledge and experience in planning and budgeting for varying delivery strategies, enumerating the target population, using acceptable consent procedures for older children and adolescents, working with the ministry of education, and developing and disseminating community education materials.

PATH/Jacqueline Sherris

Key lesson: *Experiences from the last eight years of demonstration projects were generally consistent across countries. Early demonstration projects were critical for gaining experience and support for national implementation. Lessons from recent and ongoing projects have been consistent with those experiences.*

Key lesson: *Well-designed demonstration projects assessed different delivery strategies, tested how to achieve high coverage in populations and areas with specific challenges, and focused on integration with national systems.*

LIMITATIONS OF DEMONSTRATION PROJECTS

By the very nature of their size and scope, projects have limitations which impact country learnings. The small size of the HPV demonstrations meant that they were not necessarily representative of the wider country context. Their limited scale made it difficult to assess the impact of HPV vaccination on health system functions, such as national cold chain capacity and other primary health care services. Evaluating the level of integration of HPV vaccination with the routine vaccination programme has also been challenging.

Several countries reported that the difference in funding strategies for demonstration projects and national programmes posed challenges. Four countries stated that the resource-intensive delivery strategies used during their demonstration projects might not be sustainable once the financial support provided by funders has ended. Among the 21 countries that shared opinions about

future funding availability for HPV vaccines and their delivery,18 stated either considerable uncertainty or a decision not to scale up.

Significant challenges exist in scaling up from a small demonstration project to a national programme, and some stakeholders signalled concerns over a 'loss of momentum' once the project concluded. Expansion of HPV vaccine delivery after implementing demonstration projects has stalled in a number of countries; six countries that completed demonstration projects in 2010 or 2011 are no longer providing HPV vaccination. These countries reported valuable lessons learnt, but have not yet taken action towards national introduction.

Key lesson: *The small size of most demonstration projects limited learnings about cold chain capacity, impact on primary health care and integration with routine immunisations for national scale-up.*

Key lesson: *Demonstration projects using resource-intensive delivery strategies generated concerns about the sustainability of national HPV vaccination programmes. Alternative delivery strategies were rarely tested.*

Key lesson: *Demonstration projects may have influenced the momentum of, or intention by, some countries to introduce HPV vaccine nationally.*

INCREASING THE VALUE OF DEMONSTRATION PROJECTS

Findings from the review suggested that the value of demonstration projects could be increased if countries used the opportunity to test different delivery strategies. This would help them to identify approaches that are sustainable and effective and to learn how to better provide vaccines to hard-to-reach populations. Only 5 of 36 countries purposefully selected areas that included challenging or hard-to-reach target groups or tested different delivery strategies or approaches.

The opportunity to test the delivery of combined interventions with HPV vaccine – such as tetanus toxoid vaccine, deworming or vitamin A supplementation – has largely been missed. Only 13 countries reported implementing HPV vaccine delivery simultaneously with other interventions and/or testing combined vaccination with the delivery of health education messages.

Key lesson: *Countries have not yet fully taken advantage of demonstration projects, which can be used to test different combinations of vaccination venues, timing, eligibility criteria in different populations and co-delivery of other health interventions.*

A NEW FUTURE FOR DEMONSTRATION PROJECTS

In the context of increasing vaccine availability and wide sharing of lessons learnt, countries could consider foregoing HPV vaccine demonstration projects and instead opt for a phased national rollout. This approach could allow faster national introduction of vaccine, provide experience in social mobilisation and delivery while maintaining political commitment, and avoid the potential pitfall of being separated from the national immunisation programme, which has challenged some demonstration projects.

Recommendations

Based on country experience, **funders** supporting HPV vaccine programmes should:

1. **Regularly re-evaluate policy around assisting countries to gain HPV vaccine experience and ensure that policy is as flexible as possible.** Countries must consider whether to conduct a demonstration project or opt for a phased national rollout.
2. **Be aware that converting demonstration projects to a phased national rollout might accelerate decision-making for national introduction.** This approach may help maintain political commitment for HPV vaccination.

Based on country experience, **decision-makers** supporting HPV vaccine demonstration projects or national programmes should:

1. **Determine whether a demonstration project or phased national rollout is the best method to gain experience for HPV vaccine introduction.** Given the increasing ability to learn from other countries' experiences, some countries may consider foregoing demonstration projects and instead conduct a phased national rollout.
2. **Be mindful that introducing a new vaccine through a demonstration project creates distortions to normal procedures of the national immunisation programme because of the proportionally high investment made in developing, implementing and evaluating the project.** This tends to promote the establishment of vaccination approaches that operate separately from the national programme, which may not be easily scalable.
3. **Carefully plan and design demonstration projects to gain lessons relevant for national scale-up.** Project plans might include maximising opportunities to test different strategies or delivery to hard-to-reach populations, assessing integration with national immunisation programme processes and combining vaccination with other interventions.
4. **When designing a demonstration project,** anticipate and test aspects of delivery that are likely to create challenges during national scale-up, such as staff incentives or joint supply of HPV vaccines with other vaccines.

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent eight national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

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PITFALLS

HPV Vaccine Lessons Learnt & Recommendations

Pitfalls

The introduction of human papillomavirus (HPV) vaccine has the potential to save the lives of millions of women and girls worldwide. Based on a review conducted by the London School of Hygiene & Tropical Medicine and PATH, this brief highlights findings, key lessons and recommendations related to potential **pitfalls** decision-makers should consider when implementing an **HPV vaccination programme.**

Findings and key lessons

A range of pitfalls has hindered progress in countries implementing HPV vaccination. Planners can increase the likelihood of success by learning from – and avoiding – challenges encountered by others.

PLANNING AND COORDINATION

High-level political commitment is critical for implementing both demonstration projects and national programmes; those projects/programmes that did not secure this support encountered delays in vaccine importation and fund disbursement. In several cases, lack of political support also impeded social mobilisation preparations, including printing of training and community education materials, which subsequently affected the vaccine delivery schedule.

Most successful projects/programmes noted the importance of collaboration between health, education and finance ministries, particularly during the planning phase. Lack of early involvement of school representatives at national and local levels sometimes led to challenges in enumerating target populations, engaging teachers, timing school vaccinations and communicating consistent messages about HPV vaccination eligibility. Lack of early involvement by the ministry of finance at times led to insufficient or poorly timed funding and budgeting in subsequent years. Similarly, lack of strong involvement of the national immunisation programme caused problems for projects/programmes that were unable to leverage existing experience and routine systems for transportation, cold storage, reporting and human resources.

Many projects/programmes reported that not leaving sufficient time for planning challenged implementation. A range of factors was affected, including decision-making, information dissemination and funding disbursement.

Key lesson: *Lack of political commitment early in the process caused delays later.*

Key lesson: *Failure to closely coordinate with the national immunisation programme, the ministry of education and the ministry of finance challenged effective planning, social mobilisation and delivery.*

Key lesson: *Not allowing enough time for planning challenged decision-making, availability of funds and timely disbursement.*

COMMUNICATION AND SOCIAL MOBILISATION

When rumours emerged, most projects/programmes could identify communication gaps that had allowed misinformation to affect the programme. For example, where refusal rates were high, community leaders may not have been informed about HPV vaccination, which in some cases led those leaders to advise against vaccination. Inadequate training of school staff in several countries meant they could not answer questions from parents, contributing to rumours about HPV vaccine in schools.

PATH/Scott LaMontagne

Some countries underestimated the power of negative media exposure. While most mentioned the importance of including strategies in planning documents to address rumours, in practice none reported having a crisis communications plan. In some instances, rumours gained media exposure, which may have affected coverage.

Several countries faced challenges with HPV vaccine acceptance in private schools because those schools were not engaged early or sufficiently in social mobilisation activities. Private schools required more information and time for communication with parents than government schools.

Key lesson: *Not engaging, or engaging too late, with local community leaders derailed social mobilisation efforts in some cases.*

Key lesson: *Insufficient training of school staff and lack of a crisis communications plan perpetuated the spread of rumours.*

Key lesson: *Failure to engage sufficiently or early enough with private schools led to resistance by some school leaders and parents.*

DELIVERY

Reaching out-of-school girls posed a challenge for many projects/programmes. Those without specific strategies generally failed to obtain high coverage in these populations. This review demonstrated that specific efforts are needed to identify and mobilise out-of-school girls. Those projects/programmes that only made vaccination available at nearby health facilities for out-of-school girls and/or did not employ mobilisation strategies generally reported low uptake.

Demonstration projects that failed to conduct accurate enumeration or implement eligibility criteria appropriately were unable to correctly calculate coverage. In many cases, this was a result of rushed planning or inadequate training of enumerators.

Recommendations

Based on country experience, decision-makers wanting to avoid pitfalls for future HPV vaccine programmes should:

1. **Secure political commitment early in the planning process.** This can facilitate implementation and garner support from communities, teachers, parents and girls.
2. **Closely coordinate planning and delivery with the national immunisation programme, schools, the ministry of education and the ministry of finance.** Ensure that adequate time is allowed for planning, as support from these partners can significantly improve communications, funding and delivery.
3. **Train teachers and community leaders to answer questions and combat rumours.** Social mobilisation efforts can be derailed by rumours that are allowed to take hold.
4. **Develop a crisis communications plan to address rumours in communities and media.** Having risk mitigation strategies in place can help dispel rumours quickly.
5. **Allow adequate time for private-school coordination.** Private schools require more time and information for decision-making and engaging parents.
6. **Develop additional delivery strategies to reach out-of-school girls.** Simply making the vaccine available at health facilities is not enough to ensure uptake.
7. **Ensure adequate time and capacity to conduct proper enumeration.** Failing to adequately calculate the target population can lead to inaccurate coverage estimates.
8. **Ensure sufficient funds for vaccine delivery.** Failing to secure and distribute financial resources on time can result in low coverage.

Key lesson: *A limited focus on developing and evaluating strategies to deliver HPV vaccine to out-of-school girls led to low coverage in that group.*

Key lesson: *Failure to correctly enumerate target populations resulted in difficulties in accurately estimating coverage.*

About this project: Since 2007, countries have been gaining knowledge about how best to deliver HPV vaccines through demonstration projects and national introductions. To aid decision-makers, the London School of Hygiene & Tropical Medicine and PATH conducted a review of HPV vaccine delivery experience in 37 low- and middle-income countries. These activities represent 8 national programmes and 55 demonstration projects – some of which implemented multiple delivery strategies – resulting in 72 distinct vaccine delivery experiences.

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7 Discussion and conclusions

7.1 Summary of key findings and implications

The four studies in this PhD combine to address specific gaps in the available evaluations of HPV vaccine introduction in Tanzania and other low-resource settings at the following levels:

- **The individual level**: The potential impact of the HPV vaccine on HIV incidence (**Objective 2**: To analyse associations between HPV and HIV acquisition).
- **The health system level**: The impact of the vaccine on other routine health services (**Objective 3**: To investigate the impact of an HPV vaccine campaign on routine primary healthcare service provision in Kilimanjaro region, Tanzania).
- **The population level:** How to maximise HPV vaccine coverage and adherence (**Objective 1**: To conduct a systematic literature review of factors influencing adherence to multi-dose vaccines in adolescents; and **Objective 4**: To collect the lessons learnt from HPV vaccine demonstration projects and national programmes in LAMICs).
- **The country/ regional level:** Tanzania's HPV vaccine introduction within the broader global context – similarities and differences in lessons learnt across the world and in the African region. (**Objective 4**: To collect the lessons learnt from HPV vaccine demonstration projects and national programmes in LAMICs)
- **The global level:** How to accelerate HPV vaccine introduction, encourage scale-up from demonstration projects to national programmes and sustain national programmes long-term (**Objective 3**: To investigate the impact of an HPV vaccine campaign on routine primary healthcare service provision in Kilimanjaro region, Tanzania; and **Objective 4**: To collect the lessons learnt from HPV vaccine demonstration projects and national programmes in LAMICs).

The key findings and implications of the four studies are summarised below. A larger proportion of the discussion focuses on findings and implications at the global level, reflecting the relative scale of the HPV lessons learnt project (Objective 4) in comparison to the studies conducted for objectives 1, 2 and 3.

7.1.1 Inconsistencies in observational studies prevent conclusions on the potential impact of the HPV vaccine on HIV acquisition (Objective 2; Chapter 4)

HPV vaccination programmes have already had a demonstrable population-level impact on HPV infection and HPV related disease[1,2]. Evidence of a consistent causal association between HPV infection and subsequent HIV acquisition could potentially increase the cost-

effectiveness of HPV vaccine, may enhance the political will to prioritise, introduce and sustain HPV vaccine delivery in LAMICs and increase the availability of funding from international partner organisations to do so. HPV infection could plausibly increase HIV acquisition by creating additional entry points for HIV or a favourable immunological environment in the cervix for HIV acquisition[3-5]. There is strong evidence of cofactor effects of other STIs on HIV transmission from a large number of observational studies[6-12]. At least eight other similar observational studies report a positive correlation between HPV infection and increased HIV acquisition. However, the findings from our large matched case-control study in East African women did not support the association. Our study of 37 HPV genotypes found no evidence of an association between HPV prevalence, persistence or clearance and subsequent HIV acquisition.

Inconsistencies in observational studies examining the association between HPV and HIV incidence, therefore, preclude a definitive conclusion on the association of HPV and HIV acquisition and on the potential impact that national HPV vaccine programmes may have on HIV incidence (Objective 2; Chapter 4).

The limitations described in Chapter 4, many of which are inherent in observational studies may be the reason for inconsistencies between study findings. Data are relatively limited, often because, at the time that many HIV acquisition studies or trials were conducted, it was too costly to conduct HPV genotyping or more simple HPV detection techniques were not available. All analyses to date have therefore relied on retrospective testing of cervical samples. Investigators from other large cohort studies where HIV incidence was measured could be encouraged to also investigate the association with HPV if suitable samples have been collected and stored. However, ideally, any future observational studies must be designed to prospectively sample women at frequent intervals in order to improve the classification of HPV infection, clearance and persistence.

Another way of further investigating this potential association would be to develop biomarkers of the different stages of HPV infection in order to distinguish (i) true female genital HPV infection from recent deposition of HPV from males in the female genital tract, (ii) persistent infection from (repeated) re-infection and (iii) genotype-specific clearance from viral latency. Improved classification of HPV infection and more regular sampling prior to HIV seroconversion may limit non-differential misclassification and bias in the results of any future observational studies. However, residual confounding of the association between HPV and HIV acquisition by sexual behaviour is likely to remain a problem. The only way to truly determine causality may be to perform a randomised controlled trial of HPV vaccination for HIV prevention[13].

There are many challenges in designing a trial of HPV vaccination for HIV prevention. Firstly, there is no evidence that the association between HPV and HIV acquisition differs by high or low risk HPV genotypes. If HPV infection doubles the risk of HIV acquisition, as indicated in some observational studies, the effect of HPV vaccines on HIV incidence may still be small because none of the vaccines offer protection against all 40 sexually transmitted HPV genotypes. The bivalent protects against 2 genotypes, the quadrivalent vaccine against 4 genotypes (both of these vaccines offer some evidence of cross-protection to at least two other genotypes), and the nonavalent protects against nine genotypes. Although the nine genotypes are highly prevalent and make up a large proportion of HPV infections, there are 31 other genotypes that may contribute to an increased risk of HIV acquisition, despite vaccination. In our case-control study, 52% of cases and 49% of controls had detectable HPV infection of any genotype at the visit prior to first detection of HIV seroconversion; only half of these infections were nonavalent vaccine types (prevalence of nonavalent vaccine types at s-1 visit was 28% in cases and 26% in controls; Table 4.3).

We can calculate the potential effect size likely in a trial using the population attributable fraction (PAF). The equation to calculate a PAF is as follows (where 'p' is the proportion of the population exposed and 'RR' is the estimated risk/rate ratio):

$$\mathbf{PAF = p(RR - 1) / [p(RR-1) +1]}$$

The PAF is the proportion of HIV infections that would be averted if the exposure, HPV vaccine-type infection, were removed (assuming 100% vaccine uptake and efficacy). The PAF depends on the strength of the association between HPV and HIV, and the prevalence of HPV vaccine genotypes. In one study, women infected with any HR HPV infection (12 genotypes) were 2.3 times more likely to have acquired HIV by the end of the study compared to HPV negative women in adjusted analysis[14]. The very high prevalence of HR HPV genotypes in the study population, 49%, led to an estimated PAF of HIV attributable to HR HPV of 28%. Another study estimated an adjusted effect of any HR HPV infection on HIV acquisition of 1.56, the prevalence of HR HPV in HIV positive women was 27%, and therefore the PAF, calculated as the potential percentage of HIV infections attributable to HR HPV infection, was 10%[15]. Current vaccines protect against a maximum of 9 genotypes and studies indicate a high prevalence of infection with non-vaccine types, therefore the likely measurable impact of HPV vaccination on HIV infection in a trial could be quite small.

Secondly, implementing such a trial is ethically challenging given that HPV vaccines have a proven benefit against HPV acquisition and HPV-related disease. The trial would have to be conducted in older girls who would not have otherwise received the vaccine in a government

programme, given perhaps as phased roll-out (e.g. through a step-wedged design or through cluster randomisation). This could imitate a phased delivery of a catch-up campaign.

The trial would also have to be of sufficient duration to allow girls to become sexually active. The duration of follow-up necessary to allow girls to become sexually active would be shorter if older girls are enrolled, compared to enrolment of young adolescents. However, older girls are more likely to have passed sexual debut and to have acquired some HPV genotypes and therefore the HPV vaccine may be less effective in preventing HPV infection and subsequent HIV acquisition.

Thirdly, the sample size and required resources for a cluster-randomised trial design with the predicted relatively limited effect size (of HPV vaccination on HIV acquisition) would have to be large. South Africa is perhaps the only country in the world where a trial may be feasible since it has an estimated HIV incidence of 3 per 100 person years in 15-24 year olds[16]. Assuming an annual HIV incidence of 3% over 4 years, 7300 HIV negative 15-16 year old girls (100 per cluster in 73 clusters) per arm would be needed to have 90% power to detect a 20% reduction in HIV incidence, assuming 25% loss to follow up and a between-cluster coefficient of variation (k) of 0.25. The HIV prevalence in adolescents of about 6%[17] would lead us to plan to enrol a total of 7600 girls per arm in order to enrol at least 7300 HIV negative girls. An estimated 300 HIV positive girls would also be enrolled and would also receive the vaccine. However, as South Africa initiated a national HPV vaccination programme in 2014 targeting grade 4 students (9-12 year old girls), the window of opportunity for a trial of this design is rapidly closing. Additionally, given the proven effectiveness of pre-exposure prophylaxis (PreP) for HIV[18] it may be ethically challenging to withhold PreP from girls known to be at risk of HIV exposure. The incidence of HIV may therefore be much lower than previously expected in the control arm and is likely to make the trial unfeasibly large.

7.1.2 In Tanzania, health worker absence from health facilities during the HPV vaccine school-based campaign did not affect quantity of routine services provided at the facilities (Objective 3; Chapter 5)

The retrospective, controlled, before-after analysis of routine healthcare activity found no evidence that the quantity of consultations at the health facility decreased while health workers were delivering HPV vaccine in schools. Healthcare utilization is low and extremely variable in facilities in the Kilimanjaro and Arusha regions of Tanzania and this may have limited our ability to see any effect of the 'campaign week' on levels of routine services delivered at the facility. However, staff interviews also suggested that the quantity of

consultations was not affected in the campaign week compared to a 'normal' week. Staff employed strategies such as working longer hours and restricting annual leave during the campaign. Staff also reported performing tasks outside of their normal responsibilities and patients waiting longer during the campaign week in comparison to non-campaign weeks. These strategies used to mitigate the impact of the vaccine campaign on the quantity of routine consultations may have lowered the quality of care, but this was not specifically measured.

The HPV vaccine campaign was resource intensive; it required, on average, half of the health facility workforce to leave to deliver the vaccine in schools for 3 days per dose. This is in the context of a national shortage of clinical professionals in Tanzania. The impact on service provision may have been low due to low demand for healthcare. We found service utilization was about half that expected for the size of each facility's catchment population and fertility rate. This is consistent with previous research; the Countdown to 2015 study indicated that only 43% of Tanzanian women attend the recommended number of 4 or more ANC visits[19]. In a study of typhoid in Moshi in Kilimanjaro region, only 4% of the population attended a health centre for fever management; the majority of the population preferred self-management[20]. A study in southern Tanzania found that 35% of women and newborns did not visit the health centre for post-natal care (PNC)[21]. Additionally, women who had delivered at a facility were half as likely to attend one or more PNC visit than women who had delivered at home[21].

In Tanzania, poor patient-staff relationships, long waiting times, frequent stock outs of medicines and unexpected/ informal patient borne costs have been reported in the public sector[22]. Experience of low quality care during delivery is likely to have discouraged some subsequent attendance for post-natal care in the above study in southern Tanzania[21]. Low utilization of services may also be due to lack of information about the health services on offer at the facility or awareness of their importance, distance, time or financial barriers to attendance[22] or lack of spousal support[23,24].

It is encouraging that the addition of a new HPV vaccine campaign, that takes an average of 3 days but sometimes up to a week for health workers to complete, did not result in a dramatic reduction in the number of routine consultations at health facility level. We were unable to examine impact of HPV vaccine campaigns on quality of care. However, the existing challenges of low quality and low healthcare utilization in Tanzania may lead health officials and researchers to question whether even a small additional drop in quality of care while staff are absent during campaigns is acceptable. Furthermore, if healthcare utilization increases, staff may not be able to continue to mitigate the impact of the staff shortages on

the number of consultations provided. In combination with the number of other childhood vaccine campaigns e.g. polio, measles, measles-rubella, rotavirus, HPV vaccine represents a significant additional period out of the facility for vaccinators. Since HPV vaccination is likely to be scaled up to a national programme in 2017 in Tanzania, future research should expand qualitative interviews with health workers and supervisors at different levels of the health system to explore whether a school based campaign approach or any other approach to HPV vaccine delivery is sustainable in Tanzania.

In the second year of the HPV demonstration project, the Tanzanian EPI team changed the HPV vaccine delivery strategy. The EPI team reported that the cost of delivering HPV vaccine in schools, driven by the cost of per diems for health workers, supervisors and transport, convinced the government to test a 'routine delivery' model in the second year of the demonstration project. Health workers were instructed to integrate HPV vaccine delivery into their existing outreach services to communities. The coverage achieved with this strategy and the impact of this on routine heath care delivery is still unknown. However, other countries such as Bhutan, who also took this decision, have reverted back to school-based delivery after HPV vaccine coverage fell with health facility delivery[25]. Further research following the second year of the Gavi demonstration project could explore whether the more 'routine' health facility based delivery strategy alongside integration of vaccine delivery into existing outreach services is more sustainable and feasible. Interviews with staff, patients and caregivers should specifically explore and define issues on quality of care.

7.1.3 High HPV vaccine coverage has been demonstrated in LAMICs using a range of delivery strategies (Objective 4; Chapter 6)

Data from our study of HPV vaccination lessons learnt suggest that HPV vaccination is acceptable and can be delivered with high coverage in LAMICs. This study provided the most comprehensive global review of HPV vaccine delivery in LAMICs to date. Across the projects and programmes in the 37 LAMIC included in our review, 30 countries had available HPV vaccine coverage data from 49 distinct delivery experiences. Final dose coverage of 70% or more was achieved in 84% of delivery experiences (range between 51% to 100%). All but three of these coverage data points were based on a three-dose vaccine schedule as projects/programmes pre-dated the recommendation change to two doses[26]. These coverage achievements support the feasibility of delivering HPV vaccine in resource-poor settings. Even at the lowest limit of the coverage achieved (51%), there is evidence that there would still be a significant impact on incidence of HPV-related disease especially in countries with limited screening services and a high HPV prevalence[27]. It should be noted that the majority of the coverage data are from demonstration projects. These projects, with

their small size and their concentration of funding and resources, may be more likely to achieve good coverage compared to national programmes. However, there is evidence of very high coverage in national programmes in Rwanda and Bhutan[25,28].

The majority of the HPV vaccine experiences to date in LAMICs have predominantly utilised school-based delivery with vaccine also available at health facilities and/or outreach sites for out-of-school girls. In LAMICs, school enrolment rates have increased since 2006[29]. Primary school net enrolment ratios were over 80% in all but four of the 30 countries contributing final dose coverage data (3 countries were missing school enrolment data)[29]. Strategies including schools as a vaccination venue have been the most likely strategies to achieve high coverage and the least likely to achieve low coverage.

Data on health facility based 'routine' delivery approaches are limited and include strategies that involved health facility based delivery with or without integration of HPV vaccination with routine community outreach services. More data are needed to discern factors influencing the success of these 'routine' approaches. However, it is clear that a good record of achieving high coverage with childhood vaccines does not necessarily mean integration of HPV vaccine into health facility delivery will be successful, especially as the target age group for HPV vaccine often does not routinely visit health facilities. Trust in the government health programme, endorsement by the government, and acceptance of vaccines in general as "good for health" were factors identified as influencing the success of the routine delivery. Widespread social mobilisation activities advertising the availability of the vaccine at health facilities were also necessary but did not always translate into pre-adolescent girls travelling (sometimes long distances) to a health facility for vaccination.

7.1.4 HPV vaccine adherence is higher in most LAMIC than some HIC (Objectives 1 and 4; Chapters 3 and 6)

Until the above study was completed, the HPV vaccine coverage achievements detailed in the previous section (7.1.3) were largely unknown or unpublished. Adherence to multiple dose vaccine schedules has been a problem in some developed countries[30] and some international partners had assumed that this would be a problem in LAMICs delivering HPV vaccine[31]. The majority of research studies up until 2014 identified in the systematic review on vaccine adherence/ completion rates (Objective 1, Chapter 3) originated in the United States of America (USA). In some areas of the USA, as low as 27% of those who received the first HPV dose went on to receive the third dose[30]. Race, insurance status and parental healthcare seeking behaviour were found to be predictors of vaccine schedule completion.

Only two studies identified in the review included information on LAMICs and included limited information on programmatic factors such as delivery strategy.

Our study of 37 LAMICs was able to collate completion rates from 48 delivery experiences in 27 countries. Completion rates for the 3 dose schedule ranged from 73% to 99%; 28 experiences (58%) achieved >90% completion and the remaining 20 (42%) achieved between 70% and 90% completion. Two experiences with 2 dose regimens that had available data achieved >90% completion. Factors that improved adherence were reportedly: adequate registers with contact information to enable girls to be traced for subsequent doses, involvement of teachers to create and maintain these registers and good mobilisation so that girls, teachers and parents were aware of the need subsequent doses.

Given the data currently available, final dose coverage and completion may be more of an issue in some developed countries. A number of unpublished reports and coverage surveys in LAMICs indicated that a predominant reason for HPV vaccine acceptance was the fact it was a government programme 'and therefore safe'. The perceived trust in government initiatives within the health system in some countries seems to restrict problems with coverage to groups exposed to negative media or logistically unable to attend vaccination venues. In general, interviewees in the global study of HPV vaccine lessons learnt (Chapter 6) reported a high level of demand for the vaccine in environments where the population rarely accesses free, high quality care from primary health services. However, as stated, almost all of the data from LAMICs to date are from demonstration projects using school-based delivery strategies. It remains to be seen whether similar coverage and completion achievements can be scaled-up in national programmes in LAMICs using 'routine' delivery, which may not have been tested in the demonstration projects, and where resources may be more stretched.

7.1.5 The sustainability of HPV vaccination is highly dependent on the availability of funding, political will and innovative delivery mechanisms (Objectives 3 and 4; Chapters 5 and 6)

MOH EPI teams across the world reportedly chose the school-based delivery strategy for demonstration projects in their own countries following early reports that this strategy achieved high coverage[32,33], recommendations to do so from international partners, and the supply of funds to cover delivery costs from Gavi. The reported focus of the demonstration projects were to ensure countries achieved over 50% final dose coverage since this would enable them to apply for Gavi support for a national programme[34]. It is worth noting that national programme Gavi grants do not cover vaccine delivery costs.

Three countries have now changed delivery strategy from a successful school-based delivery in a demonstration project to health-facility based delivery with integration into existing outreach services. The choice of delivery strategy is now often presented as a trade-off between achieving high coverage with school-based delivery and obtaining lower coverage but at a lower cost with a 'routine' delivery model. However, there are not enough data on routine delivery to conclude that this strategy is more acceptable, always achieves lower coverage or that it costs less.

Different delivery strategies need to be tested in the same country with careful evaluation in order to gain good information to influence the decision over whether HPV vaccination is feasible long-term. Of the 49 estimates of final dose coverage in 30 countries, only 10 coverage estimates from 6 countries were the result of coverage surveys. The remaining 39 estimates were calculations based on often inaccurate denominator estimates of target populations and records of doses delivered to sometimes ill-defined target populations. For example, multiple interviewees stated that doses had been delivered to 'any girls aged 9 years old or older' when the definition of the denominator for the target population was 9-year-olds only. In countries where both survey and administrative coverage data were available, the difference between the estimates was relatively small; however, from personal observation during interviews, these limitations in data quality can translate into confusion over how the information can be used to inform plans to scale-up from small-scale demonstration projects to national programmes.

More evidence of more sustainable delivery strategies that are less financially, time and human resource intensive than the current campaigns are needed if HPV vaccine delivery is to continue in low-income settings. More sustainable options could include adaptations of health-facility based delivery strategies with or without integration into routine outreach or adapted school-based strategies that run without the current demonstration project level of funding from Gavi. An annual national campaign to deliver the 2 doses 12 months apart is only currently being tested in one country but may prove cheaper and logistically easier in other countries too. A campaign approach to vaccinate a multi-year cohort of girls every 3-4 years is planned in another country with the expectation that economies of scale in transport and per diem costs will mean this approach is cheaper per dose delivered than an annual or twice-yearly campaign.

The perceived cost of the delivery of the programme was one barrier to scale-up. Another barrier raised by key informants was imminent graduation of their country from Gavi support and therefore the imminent requirement to commit to co-financing to pay for the vaccine. Countries eligible for Gavi support have an average Gross National Income (GNI) per capita

of USD 1580 or less over the last three years and over 70% coverage for routine childhood vaccines[35]. Once average GNI per capita rises above this threshold countries are classified as 'graduating' and must commit to co-financing vaccine procurement.

There was considerable uncertainty over future funding for HPV vaccine in 20 of 28 countries with data. This uncertainty often included the sustainability of a number of newly introduced, expensive vaccines[36] e.g. pneumococcal conjugate vaccine (PCV) and rotavirus. One country that had scaled-up to a national HPV vaccination programme stated that the EPI team were attempting to bring in an 'immunisation law' to ring-fence funding for the EPI department so they could predict their yearly budget more accurately. There are efforts from WHO to create a transparent tiered pricing system for vaccine procurement[37,38], that may enable countries to negotiate directly with vaccine manufacturers more effectively, although this is anecdotally a long way from containing enough data to achieve its aim. Countries just above the threshold USD 1580 GNI per capita to benefit from Gavi, UNICEF or PAHO pooled procurement systems would benefit most from this and it may accelerate introduction[38].

7.1.6 Substantial progress has been made in HPV vaccine introduction via demonstration projects; increasing the number of national programmes should now be the focus

Prior to 2012, HPV vaccination experience was possible through direct vaccine donations from the manufacturer to the government e.g. Rwanda, Lesotho, funding through other organisations e.g. the GARDASIL® Access Program, or NGOs, e.g. the Australian cervical cancer foundation (ACCF) or PATH. Since 2012 when Gavi announced its support for HPV vaccine delivery, Gavi has become the primary conduit for HPV vaccine access for LAMICs. The decision to introduce HPV vaccine in LAMICs is reportedly now governed by the availability of a vaccine donation, funding for delivery costs, and political prioritisation.

By May 2016, 45 LAMIC had at least 6 months experience of HPV vaccine delivery. Most of the experience is in demonstration projects and only 11 LAMIC have experience with national scale delivery. Eight more Gavi eligible countries, with no prior HPV vaccine delivery experience, have either been approved for demonstration projects or have submitted applications to Gavi (Bangladesh, Benin, Burundi, Liberia, Sao Tome have been approved in 2016; Nigeria, Mauritania, Myanmar have applied or plan to).

A further 11 countries did not reach the DTP3 coverage threshold of 70% to be eligible for HPV vaccine support in 2015 but could become eligible for HPV vaccine support in future years. These countries would represent the last Gavi eligible countries with no HPV vaccine

experience. However, there has been some criticism over the limited number of LAMICs scaling up to national delivery[39]. In 2014 it was estimated there were 33 countries where the vaccine could have the highest impact (>2500 cancer cases averted per 100,000 vaccinated girls)[39]; only seven had national vaccination programmes by May 2016. Almost all of the remaining 26 countries had experience with HPV vaccine demonstration projects, yet had not applied for support for national programmes. This calls into question the value of demonstration projects in encouraging countries to begin national programmes.

There were strikingly common lessons across demonstration projects in different world regions. Interestingly, many of the common lessons learnt were reported in 2011-13 from some of the very first demonstration projects[32,40] and had been experienced with some prior school health programmes[41]. In Tanzania, a schistosomiasis control initiative in 2008 that delivered a combined intervention of praziquantel, mbendazole and measles vaccine to 7-14 year olds identified issues in delivering the intervention during examination periods, underestimation of class sizes, transport to remote areas and recording of data[41]. All of these challenges were then encountered again in the Tanzanian MOHSW's HPV vaccine demonstration project in 2014. Demonstration projects were reportedly designed to take account of the perceived limited experience within the MOHs in LAMICs in delivering an intervention to a 'novel' age group of 9-13 year old girls in schools[42]. It is still unclear how lessons learnt in prior programmes can be more effectively disseminated and utilised by the MOH to accelerate additions of new interventions. Greater synergy is obviously needed at the national coordination level. However, this is difficult when most health programmes are vertically funded and implemented[41].

The requirements and funding of Gavi demonstration projects could be restructured to encourage greater creativity in HPV vaccine delivery strategies and the testing of other delivery strategies in different populations; this may result in the development of more sustainable delivery strategies. Phased national introduction may be more successful in maintaining commitment to scale-up than demonstration projects, which were fixed 2 year projects at the end of which re-application was required for national programme support.

7.1.7 HPV vaccine delivery could be part of a wider health platform for adolescents if integrated with other services

If HPV vaccine delivery could be integrated with another service then it maybe more cost-effective, and durable in the long-term; however, it also may increase the time health workers must spend out-of-station for vaccination days.

Despite early calls to use HPV vaccine to galvanise development of an 'adolescent health platform'[31], the scope of services that have been combined with vaccine delivery is limited[41,43,44]. In many countries, there are few existing services for the age group of 9-13 year olds and little funding to develop new services. A demonstration project in Uganda illustrated that integration with routine child health days could be a successful strategy and this was then planned for the national programme. However, when external funding for child health days ceased, this then put the plans for HPV vaccine delivery in jeopardy. Existing 'routine outreach' services are often not well funded, are not uniform in coverage both geographically and temporally, and reportedly occur when the facility has money to pay staff for transport to hard to reach areas. It remains to be seen whether they can be strengthened with the addition of HPV vaccine.

Botswana, Kiribati and Vanuatu have combined HPV vaccine with delivery of tetanus toxoid (TT) vaccine in schools. Three further countries used HPV vaccination days to also deliver deworming and vitamin A supplementation. A few more delivered health education messages on reproductive health or hygiene. There have been challenges in envisaging what an 'adolescent health platform' might look like both in the international community[45] and national ministries of health[41]. School health programmes are similar to routine outreach activities and are not always uniformly implemented across the country e.g. In Tanzania, school nutrition, sanitation, deworming and counselling services were only implemented in a dispersed selection of districts within a small number of regions[41].

Although experience in integrating other services with HPV vaccine delivery is limited, it is encouraging that the concerns that combining services could affect HPV vaccine acceptability and coverage e.g. that side effects of deworming tablets may be attributable to HPV vaccines or controversy over sexual reproductive health education may transfer stigma to the vaccine[41,43], have been unfounded to date. We found no evidence that the five projects that combined an intervention to the same target group with HPV vaccine and reported coverage achievements, gained lower coverage.

HPV vaccine introduction could be used to finally address some of the many health challenges specific to adolescence. The Lancet Commission on adolescent health and wellbeing identified a massive unmet need for services addressing mental health, substance abuse, smoking, contraception, sexual reproductive health education, early marriage, school drop-out, gender equality, violence, road safety and injury[44,46]. Across sub-Saharan Africa and some of central Asia and South America, adolescents and young adults (10-24 year olds) are now 30-35% of the population. Working towards a more proportional allocation of funding for their health needs will be the only way to create a truly effective and equitable

adolescent health service or develop alternative methods to reach adolescents outside of the traditional health service model. Given the plethora of unmet needs, the limited scope of interventions combined with HPV vaccine to date is surprising and maybe reflects the complexity of some of the health problems and the scale of the additional resources needed to address them nationally[41,43]. There is also limited engagement of the adolescent population in the development of their own services[47].

7.2 The studies' strengths and limitations

7.2.1 Strengths

Sample selection and size

The sampling strategies used for objectives 2 and 3 were designed to minimise the risk of selection bias. In the study of the association of HPV with subsequent HIV acquisition (objective 2), all women who seroconverted to HIV during enrolment in the original five studies, and had an available cervical sample from at least one visit prior to HIV seroconversion were included as cases. Controls were randomly selected from among HIV negative women with available cervical samples at the same study visits as the cases. There were good retention rates in all of the five original longitudinal studies that contributed samples. In the study of the impact of the HPV vaccination campaign on routine services (objective 3), health facilities were randomly selected from 2 districts where HPV vaccination was occurring and 2 districts where the HPV vaccination programme had not yet started, proportional to the total number of facilities in the district. The sample sizes selected for objectives 2 and 3 gave good power to detect an effect if there was evidence of one.

The countries selected for data collection for objective 4 were the result of an extensive mapping exercise completed by our collaborators at PATH who had worked closely with a number of the funding agencies for demonstration projects including Gavi. We believe that it is an exhaustive list of LIC and LMIC that had at least 1 year of HPV vaccination experience by May 2015. Some upper-middle countries were included due to a consensus that their experience with demonstration projects and scale-up to national programmes may illustrate some relevant lessons for neighbouring countries in innovative delivery strategies or sustainability issues. The final list of countries has a wide geographical scope, which enabled us to make some conclusions on the generalisability of some of the lessons learnt.

Analytical methods

The analytical methods used in each objective were robust and appropriate to the available data. A qualitative synthesis, rather than a meta-analysis, was performed for objective 1, the systematic review, due to the heterogeneity in study designs and contexts. Conditional logistic regression was performed for objective 2, the association between HPV and subsequent HIV acquisition, in order to account for the matched case-control design. A controlled before-after analysis using negative binomial regression was performed for objective 3. This analysis was the most robust option given that interrupted time series analysis was not possible. It was necessary to have data from a minimum of three 'campaign weeks', not two, in order to perform interrupted time series analysis comparing the trend in the data during campaign weeks to non-campaign weeks. The use of mixed methods for objective 3 allowed the plausibility of the quantitative findings to be checked with the qualitative data and exposed a number of reasons why no effect was seen in the quantitative data.

7.2.2 Limitations

Outcome misclassification

Outcome misclassification was a potential limitation in objectives 2, 3 and 4. As discussed, in Chapter 4 (objective 2), non-differential misclassification of HPV infection status (e.g. persistence vs. reinfection, clearance vs. viral latency) may have biased the effect estimates to the null hypothesis. Classification was additionally difficult as women in the original studies had different visit schedules so cervical samples were available at different intervals. However, the majority of samples were taken at 3-6 month intervals and this is similar to all previous studies of the association between HPV infection and subsequent HIV acquisition. Sampling interval and HPV clearance/persistence classification does not explain why our results differ from previous studies.

In objective 3, the records of zero consultations in the register books could have indicated missing data where consultations took place but were simply not recorded rather than 'true zeros'. Non-differential outcome misclassification would have biased the result to the null hypothesis of no effect. Differential misclassification i.e. if reporting accuracy in register books differed during the campaign week when the staff were more busy compared to the normal week (therefore the level of 'true zeros' differed in campaign weeks compared to normal weeks), would have biased the effect estimate to the alternative hypothesis. No method of validating the extent of misclassification was available as all data collection was conducted retrospectively. Qualitative interviews suggested that the recording of data was consistent in both the intervention and control facilities in vaccine campaign weeks and

normal weeks and that there was no incentive to mis-report health care activity to the district. However, it was not possible to assess the accuracy of routinely reported data.

In objective 4, there was a potential misclassification of 'successful programmes' as coverage data were often poor quality administrative data. Where we had data from both administrative coverage and coverage surveys, administrative coverage data always over-estimated coverage achievements. This may limit the strength of our conclusions on factors associated with high coverage.

Reporting bias

Qualitative findings and conclusions on objectives 3 and 4 may have been limited by reporting bias as we were dependent on the information shared with us by health workers and EPI representatives. For objective 4, the collation of lessons learnt from HPV vaccine delivery, we often only had resources to conduct one interview with one representative from each country. There may have been some reticence by EPI representatives to share factors that were truly challenging to their project/programme for fear it would reflect badly on them or their country. Many were surprised that they had to sign a consent form, indicating that they did not really feel they were providing sensitive or confidential information. However, most interviewees talked candidly about their experience coordinating the vaccination delivery.

Confounding & unmeasured variables

Residual confounding and unmeasured variables potentially limited the quantitative analysis of objectives 2 (the association between HPV and HIV acquisition) and 3 (the analysis of the effect of the HPV vaccination campaign on routine services). Analyses of the association between HPV and subsequent HIV, objective 2, would have been strengthened if information on partner characteristics e.g. lifetime number of sexual partners or number of concurrent relationships, had been available for all women. Additionally, the variables included in the multivariate analysis were restricted to those measured in the same way across all 5 studies. We could not adequately adjust for all confounders because of sparse data. It was difficult to define some key covariates, for example 'occupation' as sex work was only a separate possible answer in one of the studies. There may have been residual confounding in the analysis due to some insensitive measurements of covariates e.g. information on STIs was not always available at the same time-points as our cervical samples. However, we were able to include similar covariates as other previous analyses of this association.

The conclusions drawn from objective 3, the impact of the campaign on routine health care, were confined primarily to the impact on the quantity of services as qualitative interviews had not been designed to specifically assess quality of care. Logistical and budget constraints limited the number of interviews with health workers. For financial and logistic reasons, it was not possible to add interviews to address some of the emerging questions around the campaign's impact on patient experience at the facility or to include facility exit interviews with health service users.

7.3 Future research

7.3.1 The impact of HPV vaccination on HPV infection in Tanzania

There are currently no data from LAMICs to indicate the potential impact of HPV vaccination on HPV prevalence or related disease in the population. Evidence of the extent of a country-level impact on HPV related disease could be used to advocate for prioritising funding of HPV vaccination programmes e.g. in Tanzania where there are multiple competing priorities on the EPI budget (IPV and Measles campaigns in 2017). Evidence of a measurable impact of HPV vaccine on HPV prevalence may also elucidate the coverage needed to achieve herd immunity in low-income settings where there may be different sexual behaviours and baseline HPV prevalences compared with western nations[2,48,49]. The conclusion from existing research in Australia, USA and the UK is that 50% HPV vaccine coverage is necessary to achieve some level of herd immunity in men and some older women[2]. This could be different in sub-Saharan Africa where there is less heterogeneous mixing of communities and age groups[49]. In sub-Saharan Africa, some very rural, isolated and/or tribal communities are unlikely to mix with the rest of the population and age-discordant sexual relationships are more common. The equity of a delivery strategy that accesses only 50% of the population may be questionable but the coverage target in LIC to achieve some level of herd immunity and equity, is unknown and requires more research.

A study in sub-Saharan Africa to replicate some of the existing impact studies in western countries is needed to assess the impact of HPV vaccination on population HPV prevalence in men and women of different age ranges. An opportunity to conduct this study may surface if Tanzania is granted support from Gavi for a national HPV vaccination programme in 2017. A proposal for repeated cross sectional surveys of a representative population sample of men and women 13-24 years of age is being developed, with a potential additional component for sampling hard-to-reach groups e.g. pastoralists, who may attain lower vaccine coverage than the national average.

7.3.2 Evaluation of 'routine delivery' strategies, factors influencing success and sustainability

Data collection for objective 4, lessons learnt from HPV vaccine demonstration projects and national programmes, had to conclude before the evaluations of Tanzania and Uganda's 'routine' delivery strategies had been completed. Research is needed on how a health facility based HPV vaccine delivery strategy might actually function in reality and whether these 'routine' strategies gain good coverage and are actually sustainable in the long-term.

7.4 Conclusions

There is now a large evidence base to support the rationale for HPV vaccine introduction and its successful delivery in LAMICs, which currently suffer the heaviest burden of cervical cancer disease. Our observational study provided results on the association between HPV and subsequent HIV acquisition, which stand in contrast to previous studies and it is still unclear whether HPV vaccination programmes could also indirectly impact HIV incidence. However, HPV vaccination is highly effective against HPV-related disease and can be delivered with high coverage in low-resource settings. We found no evidence that HPV vaccine campaign activity affected the quantity of routine health care consultations provided at the facility despite a shortage of health workers. The effect of HPV vaccine introduction on the quality of routine health services remains unanswered. More research is needed to determine whether additional vaccination campaigns are sustainable or whether other more sustainable options for vaccination delivery in under-resourced health systems are needed and what their characteristics might be.

To date, HPV vaccine delivery in low resource settings has experienced fewer barriers and challenges than expected. Lessons learnt and recommendations for countries introducing new HPV vaccination programmes or scaling up from demonstration projects to national programmes are now collated and available. Trials are now commencing to investigate the immunogenicity of a one-dose schedule. If one dose of HPV vaccine proves adequate and can lead to a further reduction to the recommended schedule, it should be logistically easier to initiate and to sustain. In the meantime, Gavi funding structures could encourage phased national delivery or national programmes rather than demonstration projects in order to accelerate vaccine introduction. Sustainable delivery strategies can be tested in phased national programmes, whilst the political commitment to scale up is maintained.

It is clear that if funding is available, LAMICs can effectively introduce the HPV vaccine, an easy and acceptable public health intervention, that has the potential to prevent a high burden of a serious disease which affects the most productive years of a woman's life.

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8 Annexes

Annex 1: Ethical approvals from the MRCC (Tanzania) and LSHTM (Objective 3)

THE UNITED REPUBLIC OF TANZANIA

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05th March 2015

Katherine Gallagher
MITU
C/O Mr John Changalucha
NIMR Mwanza
P O Box 1462 MWANZA

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Assessing the impact of HPV vaccine introduction on routine primary health care activities in North Eastern Tanzania, (Gallagher K *et al*), whose Local Investigators is Mr John Changalucha NIMR Mwanza, has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health & Social Welfare and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Sites: Kilimanjaro and Arusha regions.

Approval is for one year: 5th March 2015 to 04th March 2016.

Name: Dr Mwelecele N Malecela

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Dr Margaret E Mhando

Signature
Ag CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL WELFARE

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Observational / Interventions Research Ethics Committee

LSHTM

6 March 2015

Dear

Study Title: A study to assess the impact of HPV vaccine introduction on routine primary health care services in NW Tanzania

LSHTM Ethics Ref: 8856

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	PROTOCOL_HWI study sept 2014_v.1.0.docx	11/12/2014	1.0
Information Sheet	Annex 3_HWI Study ICF - ENGLISH version 0.2.doc	15/12/2014	2
Information Sheet	Annex 3_HWI Study ICF - SWAHILI v.0.2.doc	15/12/2014	2
Investigator CV	CV D.Watson-Jones_Jan2015	26/01/2015	1
Investigator CV	CV Kate Gallagher Nov 2013 (2)	26/01/2015	1
Covering Letter	Cover letter_HWI Study ethics application ammendment 05March15	05/03/2015	1.0
Information Sheet	Annex 3_HWI Study ICF - ENGLISH version 0.3	05/03/2015	0.3
Information Sheet	Annex 3_HWI Study ICF - SWAHILI v.0.3	05/03/2015	0.3
Information Sheet	Letter to the Regions/Districts requesting support and permission	05/03/2015	0.1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Annex 2: Informed consent form (Objective 3)

The Health Worker Impact (HWI) study – A study of the impact of HPV vaccine introduction on health care workers and routine health services

INTRODUCTION

We are conducting research on the impact of the Human papillomavirus (HPV) vaccination programme on health care staff workload. We are doing this study because HPV vaccine is a new vaccine and the best way to deliver it in Tanzania is not yet fully understood. We would like to invite you to participate in this study in order that we can understand how HPV vaccination activities affect your workload.

This research is being conducted by the National Institute for Medical Research (NIMR) Mwanza centre and the Mwanza Intervention Trials Unit (MITU) in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM). The study has been approved by the Tanzania Medical Research Coordinating Committee and by the London School of Hygiene and Tropical Medical ethics committee.

This form contains information about the study. After reading this you will be able to decide whether you want to take part in this study. If you decide to take part, we will ask you to sign this consent form.

Please note that:

- Your decision to take part is entirely voluntary. It is completely up to you to decide whether to take part in this project.
- You can decide not to take part in the study without fear of consequences, and do not have to supply a reason.
- If you decide to take part, you may stop of the interview at any time without giving a reason.
- If you decide to take part, your involvement will be entirely confidential and your identity will be kept secret.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to explore health workers' experience of delivering HPV vaccine and whether the introduction of HPV vaccination affected workload in the health facility.

RESEARCH PROCEDURES

If you decide to participate, you will be asked to take part in a short interview today, with no further commitment. You will be asked a series of questions about yourself and your experiences at work during the time that the HPV vaccination project was being delivered. It should take no longer than 30 minutes. The interview will be conducted by a trained interviewer. Everything you tell us will be confidential and anonymized. Your involvement in the study will be confidential, the researchers here are the only people who will know you took part.

HOW WILL THE INFORMATION I GIVE BE USED AND KEPT PRIVATE?

All information collected in this study will be kept securely and confidential in a locked location. Your name and details will not be recorded on the notes or, if you consent to recording of the interview, in the recording. Analysis will only be done using the study number and your identity will remain private and confidential. Reports about the study and results will be presented to the organizations that are working together for this study including local government, and at scientific meetings. Results of this study may also be published in scientific journals. Presentations and

publications of the findings of this study will not include any information which allows you to be identified as one of the study participants.

WHAT ARE THE RISKS OF TAKING PART IN THIS STUDY?
We do not expect that you will experience any harm by taking part in this study.

WHAT ARE THE BENEFITS OF PARTICIPATING?
You will have a chance to ask questions about HPV vaccination. We hope that this research will provide useful information to the Tanzanian Ministry of Health and Social Welfare for a future HPV vaccination programme.

ARE THERE COSTS ASSOCIATED WITH PARTICIPATING IN THIS STUDY?
There are no costs to you for participating in this study. Everyone who participates in the study will receive Tsh 5,000 after the interview. This is compensation for your time related to your participation in the study.

LENGTH OF PARTICIPATION
The interview should take no longer than 30 minutes.

WHOM CAN I CONTACT IF I HAVE QUESTIONS OR NEED ADDITIONAL INFORMATION?
If you have any questions now, please ask us. If you have any questions later, you can also contact:

- **Ms Kate Gallagher**, Mwanza Intervention Trials Unit, National Institute for Medical Research, P.O. Box 11936, Mwanza, Tanzania, Telephone: 028-250 0019, Mobile: 0754 310 366
- Chair, c/o **Mr Mansuet Temu**, Lake Zone Institutional Review Board, National Institute for Medical Research, P.O. Box 1462, Mwanza. Tel:+ 028 2541935

AGREEMENT TO JOIN THE STUDY
I have read this form, or had it read and explained to me. I understand the information and was able to ask all my questions. I have been given a copy of this form.

I voluntarily agree to participate in this study by signing below.
I grant permission for audio recording equipment to be used during my interview YES/NO*
(Delete as appropriate)
I agree to the use of direct quotes from my interview in published results as long as they are not attributed to my name or any other identifiable information YES/NO*
(Delete as appropriate)

Participant name (**print**)	Participant signature	Date
Name of study staff conducting consent (**print**)	Study Staff signature	Date

Participant Identification number: _____ *(To be completed by study staff)*

Annex 3: Quantitative data collection forms (Objective 3)

District Information Form 1

1	District *(please circle)*	Moshi DC = 1 Hai = 2 Arusha = 3 → *Skip to Qu 4.* Meru = 4 → *Skip to Qu 4.*			*district*
2	Total eligible population for HPV vaccine dose 1 **in 2014** (>9 year olds in School form 4 and 9 year olds out of school)				*disvpopn*
3	Total number of girls vaccinated in the district **in 2014**	_____ dose 1		_____ dose 2	*disvd1* *disvd2*
4	Health campaigns involving outreach activities January 2014 – December 2014:	Number of staff involved **per health facility**	Dates	Duration	
	e.g Deworming in schools	*1 nurse assistant*	*1st July*	*1 day*	
5	Staff training activities January 2014 – December '14:	Number of staff involved per health facility	Dates	Duration	
	e.g. HPV vaccine training				
6	Code of data collector		|___|___|___|		*intcode*
7	Signature of data collector	Date (dd/mmm/yr)	|___|___|-|___|___|___| -2014		*date*

Health Facility Description Form 2

1	Health Facility Name					*facility*
2	Facility Reg. No.					*reg*
3	District					*district*
4	Ward					*ward*
5	City/town/village					*site*
6	Tracing information/ extra directions					
7	The number of staff who routinely work at the facility *Count staff by the highest role they operate as e.g. if a nurse assistant is also the cleaner, count them as a nurse assistant not a cleaner.* *Please specify 'other'*	Cadre	Number of staff	Number full time	Number part time	
		Doctor				*hfdocfte, hfdocpte*
		Nurse				*hfnfte, hfnpte*
		Nurse Assistant				*hfnafte, hfnapte*
		Midwife				*hfmidfte, hfmidpte*
		'Other clinical staff' _____				*hfostaff*
		'Other' _____				
		Comment:				
8	The number of staff who went out to schools to delivery HPV vaccine in 2014:					
9	The number of primary schools in the facility's catchment area at which HPV vaccine was delivered in 2014					*primsch*
10	**Dates** of HPV vaccine outreach (when the staff left the Health facility to go to schools to deliver the vaccine):	Dose 1 delivered: ___ May 2014 - ___May 2014 Dose 2 delivered: ___ Nov 2014 - ____ Nov 2014				
11	Dates of other campaign activity or outreach days in 2014:					

11	Code of data collector		|__|__|__|	*intcode*
12	Signature of data collector	Date		*date*

Health Facility Activity Info. FORM 3

Mwanza Intervention Trials Unit

Study: HWI Study Facility _____|__|__|__| District _____|__|__|

Date	**Number of under 5 outpatient consultations**	**Number of under 5s registered for vaccinations**	**Number of first ANC appointments**	**Number of family planning consultations**	**Notes**	Date of data collection	Data collector initials
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Annex 4: Interview topic guides (Objective 3)

Topic Guide: In-depth Interviews with health workers involved in HPV Vaccine implementation

A: Experience working at the facility

Now I am going to ask you questions about your experience on working at this facility

1. How long have you been working at this facility?
2. How many days per week do you work at this facility?
3. What are your roles at this facility?
4. Is your salary enough to support your family?
5. What do you think of the salary you are getting now? (Probe: Is it paid on time?)
6. Do you work elsewhere different from this facility?
7. Do you get incentives/allowance to complete certain extra services in the facility? (Probe: Do you live on extra per diems?)
8. Do you supplement your income another way? (Probe: If yes, what do you do)

B: Workload and staffing

Now I am going to ask you questions about workload at the facility in relation to staffing

9. What do you think of the workload at this facility? (Probe: is there too much work, an average workload or a low workload)
10. Is there enough staff in the workplace? (Probe: for the workload and available number of staff, do you get free time for tea and lunch? Do you feel stretched or are you able to absorb further work in the form of health campaigns?
11. In general do you feel you have adequate training and capacity for your roles at the health facility?)
12. How do you feedback to the district? Do you feel supported/ supervised/ autonomous in executing your work? Are there targets set by the district to fill? What are they? What do you do if you have not reached a target?
13. How do you take time off/leave? Are there times of year when it is easy to take time off/ annual leave? (Probe: Were you able to get time off/leave during HPV campaigns? If No, does this also happen during other campaigns like this one?)

C: HPV vaccine implementation

Now I am going to ask you questions about HPV vaccine implementation

14. Do you feel you got adequate training, and preparation for HPV vaccine delivery?
15. To what extent were health-workers involved in the planning of HPV vaccine delivery? (Probe: Choosing when it happened and how? Would you have planned it differently?)
16. What is your overall experience with HPV vaccine implementation and your perception towards the HPV vaccine?

17. To what extent people in the community know about HPV?
18. How well do you think the awareness and education campaign went before the vaccine delivery?
19. How much work was it to deliver the vaccine in schools last year (Probe on Opinions on the school site for vaccination?)
20. Do they perform other outreach activities in schools? How does the workload compare? Why does HPV vaccine implementation differ from these campaigns?

For HPV vaccination:

21. Was there just one visit per school, or did you have to make preparatory/ follow-up visits?
22. Did you get remuneration for the HPV vaccine delivery?
23. How long did it take for vaccine delivery in one school? How many schools did they visit? Did they have enough vaccine?
24. Was there a good supply of equipment and stock for the vaccine? How does the level of supply compare to the supply of equipment for other services and other campaigns?
25. Did HPV affect other services? Are the community now more or less engaged with the health facility? Did HPV vaccine affect other vaccines? Do they think it will affect other vaccines (awareness/ demand)?
26. What experience did they have collaborating with education officials?
27. What are the personal advantages or disadvantages of being involved in the vaccination?
28. Are there any particular successes or problems with the HPV vaccine implementation?
29. Did the experience differ when you delivered the second dose compared to the first?

We have come to the end of our interview, thank you for your time and collaboration. I would like to remind you that any information that you have shared with us will be kept highly confidential and it will only be used for the research purpose.

Topic Guide: In-depth Interviews with health workers at the facility

A: Experience working at the facility

Now I am going to ask you questions about your experience on working at this facility

30. How long have you been working at this facility?
31. How many days per week do you work at this facility?
32. What are your roles at this facility?
33. Is your salary enough to support your family?
34. What do you think of the salary you are getting now? (Probe: Is it paid on time?)
35. Do you work elsewhere different from this facility?
36. Do you get incentives/allowance to complete certain extra services in the facility? (Probe: Do you live on extra per diems?)
37. Do you supplement your income another way? (Probe: If yes, what do you do)

B: Experience at the facility during HPV vaccine implementation

Now I am going to ask you questions about HPV vaccine implementation

38. What is your overall impression of HPV vaccine implementation for the last year (2014)? Would you want to be involved in delivering HPV vaccine if you could? Why/ why not?
10. How did the public respond to HPV vaccine?
11. How did it affect the people coming to the facility? (Probe: Were people aware of the existence of HPV vaccine and campaign?)
12. How did HPV vaccination activities affect the facility workload? Did it matter that one staff member was away? What did they do to overcome the gap?
13. Were staff able to take time off/leave during HPV vaccination delivery? If No, Why?
14. What is the supply of equipment/ drugs in the health centre like compared to regular vaccine supplies? Did HPV affect the supply of other vaccine equipment at the facility? Or was it timely or delayed than before?
15. Did vaccine storage equipment changed for HPV?
16. Did HPV vaccination activities affect uptake of other vaccines in the health facility? Did it increase awareness for other vaccine uptake in the facility? Or other services including other adolescent services in family planning or reproductive health?
17. What overall effect do you think HPV vaccine had on the health centre? (Probe: did it increase/decrease demand for services? Did it increase or decrease the health facility's ability to provide other routine services?

18. How did the experience at the health facility during HPV vaccination activities compare to periods of time during other vaccine campaigns e.g. the measles-rubella campaign?
19. Do you have anything that you would like to add concerning what we have discussed about HPV vaccine delivery?

We have come to the end of our interview, thank you for your time and collaboration. I would like to remind you that any information that you have shared with us will be kept highly confidential and it will only be used for the research purpose.

Annex 5: Ethical approval from LSHTM (Objective 4)

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United Kingdom
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www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Deborah Watson-Jones
Clinical Reader
Department of Clinical Research (CRD)
Infectious and Tropical Diseases (ITD)
LSHTM

23 March 2015

Dear Deborah

Study Title: Scaling of lessons and best practices from HPV demonstration programs

LSHTM Ethics Ref: 9010

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV D.Watson-Jones_Jan2015	26/01/2015	1
Investigator CV	CV Helen Burchett	26/01/2015	1
Investigator CV	CV SandraMounierJack_Jan2015	26/01/2015	1
Investigator CV	CV_Ulla Griffiths Jan 2015	26/01/2015	1
Information Sheet	HPV lessons learned project description 12Jan14	26/01/2015	1
Information Sheet	ICF_HPV Countries	26/01/2015	1
Information Sheet	ICF_NO HPV Countries	26/01/2015	1
Local Approval	Cover letter_BMGF ethics application	26/01/2015	1
Protocol / Proposal	BMGF KII PROTOCOL 26Jan15	26/01/2015	3
Covering Letter	Cover letter_BMGF ethics application ammendment March15_final	06/03/2015	3
Information Sheet	ICF_HPV Countries 05March15_v.2	06/03/2015	2
Information Sheet	ICF_NO HPV Countries 05March15_v.2	06/03/2015	2
Information Sheet	Letter from Axios to grantees_draft1	06/03/2015	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

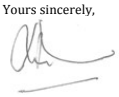
The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,



Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Annex 6: Informed consent form (Objective 4)

HPV LESSONS LEARNT PROJECT
INFORMATION SHEET
INTERVIEWS IN COUNTRIES WITH HPV VACCINE EXPERIENCE

Introduction

We are conducting research on the lessons learnt and best practices from HPV vaccine demonstration projects and national programmes worldwide. The study will be used to develop recommendations on how HPV vaccine delivery programmes can be successfully designed and integrated into national immunization programmes.

The research is being conducted by the London School of Hygiene and Tropical Medicine (LSHTM) and the Programme for Appropriate Technologies in Health (PATH).

Participation

We request your participation in this interview because we believe you may be able to contribute to our understanding about past experiences with HPV vaccine demonstration projects.

Taking part in the study is entirely voluntary and withdrawal is possible at any time without any penalty to you and without having to give a reason.

If you agree to take part in this research, we would like to ask you some questions for approximately 60 minutes.

Risks and benefits

The research will in no way inconvenience you apart from the time it will take you to participate in this interview. The information that we gather from you and others interviewed will assist us in understanding the lessons learned from HPV vaccine demonstration projects. We will write reports and other outputs based on this information, which may inform future positive developments in this area.

Confidentiality

We will maintain strict confidentiality throughout this study. Your name will not be linked to any quotes or other results of this study or included in any reports, even anonymously.

Notes taken during the interview will be stored securely; computer files will have access codes and will only be shared among study team members.

We appreciate your participation in this study. We thank you for your time and effort. If you have any questions or concerns about the study, please do not hesitate to contact Dr Deborah Watson-Jones, LSHTM & Mwanza Intervention Trials Unit, Tanzania. Email:Deborah.watson-jones@lshtm.ac.uk

The London School of Hygiene and Tropical Medicine Ethical Committee approved this study on: ……..

INFORMED CONSENT

INTERVIEWS IN COUNTRIES WITH HPV VACCINE EXPERIENCE

Research participant consent form

Principal Investigator:
Dr Deborah Watson-Jones
London School of Hygiene & Tropical Medicine
Faculty of Infectious Disease Epidemiology
Keppel Street
London
Email: Deborah.watson-jones@lshtm.ac.uk
Phone: +447447300967/ +251911028612/ +255754056066

The purpose of this form is to allow the use of your interview for research purposes (in publications or presentations). Please fill in the form according to your wishes.

Name:

Signature:

Date:

Please tick one only:

I permit the use of anonymous quotes from the interview ☐

I do not want quotes from my interview to be used directly in publications/ presentations. Information I provide should only be used aggregated with other information ☐

Annex 7: Interview topic guides (Objective 4)

Lessons learnt from HPV vaccine demonstration projects

Extension & supplement data collection: Key Informant Interview Topic Guide for countries with HPV vaccine experience

The interview will involve structured and open questions on a selection of the following topics dependent on what information is obtained from the published and grey literature review or previous interviews.

1. Decision making:
   - How was the decision made to conduct the HPV vaccine demonstration project?

2. Planning:
   - Who was involved in the planning (EPI/education?)? Was there a committee? Where there any challenges during planning?

3. **Delivery strategy:**
   - **What was the delivery strategy (target population & venue) for HPV vaccine delivery? (probe if a HF only strategy - how it worked etc.)**
   - **Did this change during the project/programme? (Why? What was the result?)**
   - **Are there plans to change the delivery strategy in the future (if the project/programme is on-going or hypothetically would they use the same delivery strategy in the future)?**
   - **Did you use a 2-dose or a 3-dose schedule? (If they have experience in both – how was the experience delivering 2 doses different (ease/cost..)?)**
   - **Timing of vaccination – was HPV vaccination performed on specific days? If it was provided on specific days - How many days? i.e. was it campaign-like?**
   - **How were girls who were absent on the day of vaccination accessed (were there 'mop-up' activities?)?**
   - **Was there a specific delivery strategy for out-of-school girls/ identified hard-to-reach girls (what was it)?**
   - **How did delivery of HPV vaccine involve the EPI programme? Challenges?**
   - **If schools delivery was used what was the role of teachers and educational staff in the delivery (organising, consent taking, follow-up of absentees, completing reporting forms?)?**
   - **Was HPV vaccine delivered with any other services (e.g. other vaccines/health education/ child health interventions…)? Lessons learnt from this?**
   - **Is there any kind of other routine outreach to schools/ the 9-13 yr old age group e.g. Td outreach? What are the benefits/difficulties in joining HPV vaccine delivery with this programme?**

4. **Vaccine management:**
   - **Prior to vaccine delivery, how was the amount of vaccine required, calculated? for both in-school and out-of school girls? Did this estimate prove accurate?**
   - **How was vaccine supplied to the delivery sites? How did the supply chain differ from that used for other EPI vaccines?**
   - **Were there sufficient supplies of vaccine and consumables at each venue?**

- **How was the waste generated by vaccination managed and disposed? How did this differ from the management of EPI vaccines?**

5. Cold Chain:
   - Was an assessment of cold chain capacity completed before implementation? Was the same EPI cold chain facilities used for HPV vaccine?
   - Were changes needed and made to the cold chain facilities for HPV (before, during or after HPV vaccine delivery)?

6. Quality/ Safety of care:
   - How were AE/SAE reported? Were there any AEs/SAEs? How were these dealt with?
   - If the vaccine was delivered outside of the health facility, were emergency kits present? Did you have any problems with safe injection procedures?
   - How were safety processes for HPV vaccine (AE/SAE reporting and safe injection procedures and training) different from what is done in the EPI program?

7. Social mobilization:
   - **Was social mobilization conducted before HPV vaccine delivery?**
   - **What were the key messages and communication materials used?**
   - **How the messages were delivered (radio/ drama/ newspaper?)?**
   - **Who delivered the key messages about HPV vaccine (was it a MOH spokesperson/ community leaders/ religious leaders?)**
   - **Who was the target audience?**
   - **When/ how often was social mobilisation done and how far in advance of vaccination with each dose?**
   - **Were vaccine recipients given incentives to attend the vaccination venue?**
   - **Were messages delivered during social mobilization integrated with educational messages about other health interventions/ other vaccines e.g. EPI vaccines?**

8. The consent process:
   - **How did parents give permission to vaccinate? Opt-in or opt-out?**
   - **How were parents informed about vaccination activities for opt-out consent/ how were parents accessed for opt-in consent? Challenges?**
   - **Was the process the same as for other routine vaccinations e.g. infant vaccinations or TT boosters in older children?**

9. Coverage/ acceptability of HPV vaccine:
   - **Do you have information on acceptability of vaccination/ refusals? How were issues overcome? What did parents say were factors that made them get their daughters vaccinated/ prevented them getting their daughters vaccinated? What were the reasons for non-vaccination? What were the reasons for not completing the 3-dose series?**
   - **Coverage of dose 1, 2 for each year of implementation? In school girls and out of school girls? How were these calculated – what was the denominator used?**
   - **What aspects of the project/programme do you think influenced coverage?**

10. Availability of health care staff:
   - How many staff were used to deliver the vaccine at each vaccination session? Did this differ between sessions at the health centre/ school/ other outreach site?
   - Were staff the same staff as those used to deliver EPI vaccines?
   - How many individuals/schools/ communities would one HW/ 1 team cover?

- How long did vaccination activities take? Did the vaccine activities affect normal work?
- Is there any evidence of the extent to which routine health care activities including routine EPI were disrupted during HPV vaccine activities?

11. Training of staff:
    - Who participated in training (District representatives/ Number of HWs/ teachers/ community members?)? Did they train others? Who conducted the training?
    - Did training reach the numbers expected/ was more training necessary?
    - When was it (how long before vaccination)?
    - How long was it? Is it now routine training or was it a one-off?
    - Was it integrated with training for routine EPI program?

12. Remuneration of staff:
    - **Were per diems used to pay staff for vaccine delivery/ to attend training/ to conduct social mobilization activities?**
    - **Were incentives to staff used/ helpful/ necessary for quality of care?**
    - **Are processes for remuneration similar to EPI vaccines? Were per diems the same amount as given for routine EPI vaccine delivery?**

13. Performance and supervision of staff:
    - What support and supervision of staff was conducted during HPV vaccine implementation?
    - Was supervision integrated with other EPI/ health facility supervision?
    - Did the level of supervision differ from routine EPI vaccine delivery? Why?

14. Monitoring & Evaluation – Reporting systems
    - How was data collected at the site of delivery on the number of girls vaccinated/ the number who received dose 2 after dose 1?
    - Was the quality of data collection assessed or supervised?
    - Were data collection forms and subsequent data management processes integrated with the national HMIS / the routine EPI reporting systems?

15. Financial support for HPV vaccine and sustainability:
    - **Who financed the vaccine?**
    - **Who financed the delivery costs?**
    - **What are plans for financing the HPV programme in the future?**
    - **Has a costing study been undertaken of the demonstration project/ national programme? Details?**

16. Scale-up and Value: If the country performed a demo/ pilot programme; has there been scale-up after the demo to more regions or national roll-out?
If yes:
    - **How was the decision made to scale-up from pilot/ demo to a national programme?**
    - **Did the experience/results from the pilot/demo influence the decision to scale up/ delivery strategy chosen?**
    - **Do you think you could have gone straight to national roll out if the funding was available?**
    - **How could the demo(s) have been more helpful/useful? If you did it again would you have designed the demo differently to make sure it was useful when planning national programme?**

- **What are the plans for HPV vaccine in the future? Continued natl programme? (Sustainability?)**

If no:

- **What are the plans for HPV vaccine delivery in the future? Another demo? National?**
- **How would HPV vaccine be delivered in the future? / how would the programme be coordinated? (Sustainability)?**
- **Will the demo experience help in planning a national programme?**
- **Do you think you could have gone straight to national roll out if the funding was available?**
- **How could the demo(s) have been more helpful/useful? If you did it again would you design the demo differently to make sure it is useful when planning a national programme?**

Lessons learnt from HPV vaccine demonstration projects

Key Informant Interview Topic Guide: Countries who have not yet implemented HPV vaccine demonstration projects.

The interview will involve structured and open questions around factors influencing the decision to implement/ not-implement HPV vaccination:

- The interviewee's role and experience in the immunization services in general and in decisions related to the HPV vaccination programme specifically.

Factors influencing the decision on HPV vaccine introduction

- Do you feel cervical cancer rates are a health priority for the country?
- How can cervical cancer be prevented? Are you aware that there is a vaccine against HPV?
- Are you aware that HPV vaccine is available through GAVI funding (free for a demonstration project, subsidised for a national programme)?
- In your view, what are the key reasons why HPV vaccine has not yet been introduced/ an application to GAVI for funding for introduction of HPV vaccine has not been made?
- Are there other interventions which are/will be prioritised before HPV vaccine? For what reasons?
- Have there been discussions in the MOH on the opportunity to introduce HPV vaccine? Who has been involved in these discussions (roles/ titles (not names))? What have been the outcomes of these discussions/ what are the key points raised by different stakeholders?
- If so, what information was needed in those discussions or what would be needed now if discussions were to take place about introducing HPV vaccine in a pilot/ national programme?
- Does the country have experience of GAVI Alliance funding? What was the experience (were there particular benefits/ drawbacks that you know of?)

Decision processes

- How are decisions made on whether to introduce new vaccines? (Probes: are there committees e.g. an immunization advisory committee? Who is involved? Are stakeholders from outside the MOH involved?)
- Which vaccines have been introduced into the national vaccination programme/ introduced in demonstration projects in the last five years? What information was required in order to introduce these new vaccines? How was the final decision arrived at? What factors influenced these decisions?